Review Article

Pediatric leukemia

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ABSTRACT

Leukemia, although a rare disease, exceeds a cause of death from many of the acute communicable diseases because of its fatal character. It is characterized by widespread, rapid, and disorderly proliferation of leukocytes. In India, leukemia is the most common childhood cancer with a relative proportion varying between 25% and 40% and continues to be the largest contributor to cancer-related mortality in children. This paper reviews the etiology, risk factors, diagnosis, oral complications, and prognosis of pediatric leukemia.

Key words: Acute lymphocytic leukemia, diagnosis, etiology, india, oral complications, pediatric leukemia, prognosis

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INTRODUCTION

Leukemia is a malignancy with disseminated proliferation of immature or blast cells of the bone marrow, which replace the normal marrow elements and tend to accumulate in various tissues of the body.[1] Leukemia was first identified by researchers, Virchow and Bennet in the year 1845.[2] European physicians in the 19th century were the earliest observers of patients who had markedly increased white cell counts. The term "Weisses Blut" or "white blood" emerged as a designation to this disorder. Later, the term leukemia, which is, derived from the Greek word "leukos," meaning "white," and "haima," meaning blood was used to indicate the disease.[3]

Leukemia, although a rare disease, exceeds a cause of death from many of the acute communicable diseases because of its fatal character.[4] It is characterized by widespread, rapid, and disorderly proliferation of leukocytes and their precursor and the presence of immature leukocytes in the blood often in very large numbers unexceptionally at some time during the course of the disease.[5] Leukemias are usually classified according to their clinical behavior (acute or chronic) or histogenesis (myeloid or lymphocytic/lymphoblastic). Hence, there are four main types of leukemia, namely chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL), and acute myelogenous leukemia (AML).

According to the Leukemia and Lymphoma Society, USA, there were approximately 13,410 new cases of AML, 5,200 new cases of ALL, 4570 cases of CML and 15,110 cases of CLL diagnosed in the year 2007-2008 in USA. Again, this society has reported in the year 2010-2011 that blood cancers would account for 9.0% of the 1,529,560 new cancer cases diagnosed in the US this year. Leukemia alone[6] comprises 27.5% of cancers affecting the children aged 0-19 years in United States. It further states that every 4 min, one person in the United States is diagnosed with a blood cancer. Even in Britain the second largest contributor to mortality from childhood cancer is leukemia.[7]

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In India, leukemia is the most common childhood cancer with a relative proportion varying between 25% and 40% and continues to be the largest contributor to cancer-related mortality in children.[8] Sixty to 85% of all leukemias reported are acute lymphoblastic leukemia. Reported annual incidence of ALL is approximately 9-10 cases per 100,000 population in childhood.[9] Compared to the developed world, the biology of ALL appears different in India, with a higher proportion of T-cell ALL (20-50% as compared to 10-20% in the developed world), hypodiploidy and translocations t(1;19), t(9;22), and t(4;11), all of which contribute to a poorer prognosis of this leukemia.[10-13]

The cause of ALL remains largely unknown, although many conditions may influence its development. Some of the risk factors which are important in the pathogenesis of leukemia are; ionizing radiation; chemicals; (e.g., benzene, heavy metals, pesticides, petroleum distillates), drugs (chemotherapeutic drugs agents, alkylating agents, and etoposide, especially when used with radiotherapy); viral infection and genetics.[14]

ETIOLOGY

Genetic basis

In ALL, chromosomal translocations occur regularly. It is thought that most translocations occur during prenatal development. These translocations cause a rearrangement of genes, which in turn to transformation of proto-oncogene into an oncogene. The oncogene causes leukemia either by stimulating cell division or by inhibiting the programmed cell death called apoptosis. A translocation can activate a proto-oncogene by two different mechanisms. A more frequent event is a merger of two genes to form a fusion gene that produces abnormal chimeric protein inducing leukemia. As an example, translocation t(1; 19) in ALL creates the fusion of E2A (immunoglobulin enhancer-binding factors E12/E47) and PBX1 (pre-B-cell leukemia transcription factor 1) genes. In the E2A-PBX1 fusion, protein transactivating domains of E2A are joined to the DNA-binding domain of PBX1, which alters the transcriptional properties of the PBX1 transcription factor.[15,16]

Inactivation of a tumor suppressor gene is another event that may initiate leukemia. Tumor suppressor genes are essential for normal cell development, and they prevent carcinogenesis. Very few tumor suppressor genes have been reported in acute leukemias. Screening for chromosomal regions with loss of heterozygosity is one way to track novel tumor suppressor genes. In childhood ALL, short arms of chromosomes 9 and 12 (in about 30-40% and 25-30% of the patients, respectively) are the regions that most frequently show loss of heterozygosity.[17,18]

The other mechanism by which a translocation causes leukemia is transfer of a normally quiet transcription factor gene to the neighborhood of active promoter or enhancer elements, which accelerate the function of the gene. For example, in translocations t(8;14), t(2;8), and t(8;22) in Burkitt leukemia, the gene encoding the MYC transcription factor is exposed to the enhancer elements of an immunoglobulin gene. These enhancer elements cause overexpression of the MYC gene, which is important in the regulation of cell division and cell death.[19] Further characterization of these genes revealed that they are often involved directly or indirectly in the development and homeostasis of normal blood cells, and that abnormal protein products of fusion genes created by specific translocations and inversions can deregulate proliferation, differentiation or programmed cell death (apoptosis) of blood cell precursors.[20,21]

Evidence in support of prenatal origin of ALL in children comes from the observation that the immunoglobulin or T-cell receptor antigen rearrangements that are unique to each patient's leukemia cells can be detected in blood samples obtained at birth. Similarly, studies have observed that children with ALL characterized by specific chromosomal abnormalities had blood cells carrying the abnormalities at the time of birth.[22-24] Further, genetic studies of identical twins with concordant leukemia also support the prenatal origin of some leukemia.[24] As an association between certain dermatoglyphic patterns and specific chromosomal aberrations has been observed, dermatoglyphic traits can be used as a diagnostic tool in medicine.[22] In pediatric leukemia, studies have indicated that most chromosome translocations and preleukemic clones arise during fetal hematopoiesis with secondary genetic events that occur postnatally.[25] However, there is little evidence that ALL is heritable.

RISK FACTORS

Ethnicity

Indian population being multicultural and multiethnic have conserved their gene pool because of the caste system and intra caste marriage requirement. Hindus (including Sikhs, Buddhists, Jains) constitute 85% of the population, and 15% religious minorities are comprised of Muslims and Christians. The records of leukemia comprise 86.5% of Hindus and rest for other religions which are in accordance with their population.[26]

Blood groups

The significant presence of AML has been observed in all types of blood groups but not with other types of leukemias. Data have shown a significant association of ABO blood groups and different cancers like duodenal ulcer,[27] gastric cancers[28] etc. Macmohan *et al.* have shown a tendency of leukemia to occur less frequently in persons of group O than in persons of group B and

AB.[29] However, Modak *et al*. nullifies the concept of tendency of any particular blood group toward leukemia.[26]

Sex disparities

Males show a higher risk for all forms of leukemia with the overall ratio of 1:8.1. There is no explanation for females to be protected against leukemia.[30] In a study from Haryana by Kumar *et al*., there were 70.2% children and 29.8% adult patients of ALL in which male to female ratio was 2.03:1.[31]

Geographic

It has been proposed that T-cell ALL predominates in economically disadvantaged areas, but with urbanization, industrialization, and increasing affluence incidence of ALL have increased.[32] ALL is reported to be the most frequent in the south[33] and intermediate in the East, West,[34] and central India.[35] Interestingly, the incidence of ALL is lesser in east India[36] as well as Northern areas.[37] However, this has be determined if this is a true difference or a registration artifact (cancer registration in the North East started in 2003).

Age

The age distribution of children of ALL in developed countries shows a very marked early peak between 2 and 5 years, followed by a small peak between 11 and 15 years and the median age of 4 years.[38-40] There has been a gradual increase in the incidence of ALL in the past 25 years.[41]

Ionizing radiation

Ionizing radiation is considered as a known cause of ALL. The risk is also higher for those exposed at an earlier age[42] and secondary leukemias in the individuals treated by radiotherapy.[25] Radiation from nuclear power plants[43] and X-ray examinations of pregnant women may be associated with increased risk of childhood ALL.[44] Postnatal exposure of infants for diagnostic X-ray increased the risk by 60%.[45] and was associated with of ALL, specifically B-cell ALL but no AML or T-cell ALL.[46]

Pesticides

Home use of different multiple pesticides put the children into risk of developing ALL. Exposure of expecting mothers to solvents, paints, or thinners increased the risk of ALL in children. The father's exposure to plastics before conception was also associated with greater risk. Furthermore, time of exposure is an important factor.[47]

Electromagnetic field

Children living near high voltage power installations were more likely to be found to have leukemia than other children.[48] One recent study found that risk of leukemia was elevated when exposure to electromagnetic field was consistent over the term of the pregnancy and in cases where the design of the water system in the home led to "ground currents" from connections between plumbing pipes and the grounding for the electricity.[49]

Association with genetic diseases

Children with trisomy 21 (i.e., Down syndrome) are up to 15 times more likely to develop leukemia than normal children. Other less common preexisting chromosomal abnormalities have been linked to leukemia, included are Klinefelter's syndrome, Bloom syndrome, Neurofibromatosis type I, Schwachman syndrome, ataxia telangiectasia syndrome, Wiskott-Aldrich syndrome, and Fanconi's anemia. Lymphoid malignancies, with a predominance of T-ALL, have been reported in patients with ataxia-telangiectasia, an autosomal recessive disorder characterized by increased chromosomal fragility.[50-53]

Infection

Evidence supports the hypothesis that an infection is involved in the etiology of ALL in children, particularly those cases seen in children between 2 and 5 years of age.[54-56] However, some studies show a protective effect[57] and others suggest the opposite.[58] Association of human T-cell lymphotrophic virus type I with adult T-cell leukemia, epstein-Barr virus with mature B-cell ALL, and human immunodeficiency virus (HIV) with lymphoproliferative disorders has also been described.[59,60]

DIAGNOSIS

ALL is diagnosed with medical history, physical examination, peripheral blood smears, bone marrow biopsy, cytogenetics, and immunophenotyping. The higher the white blood cell (WBC) counts, the worse the prognosis.[61] Pathological examination, cytogenetics (in particular for the presence of Philadelphia chromosome), and immunophenotyping establish whether leukemia is myeloblastic (neutrophils, eosinophils, or basophils) or lymphoblastic (B lymphocytes or T lymphocytes) and identify the cell surface antigens expressed by the tumor cells. RNA testing can establish how aggressive the disease is; different mutations have been associated with shorter or longer survival. Medical imaging can find metastasis to other organs commonly the lung, liver, spleen, lymph nodes, brain, kidneys, and reproductive organs.[62,63]

Peripheral blood smear

Microscopic examination of leukemia affected tissue shows diffuse infiltration and destruction of the normal host tissue by sheets of poorly differentiated cells with either myelomoncytic characteristics or lymphoid features. Blast cells are seen on the blood smear in majority of cases.[64]

Bone marrow biopsy

Bone marrow biopsy is normally performed in conjunction with the peripheral blood smear because some patients

may undergo through an aleukemic phase in which atypical cells are absent from the circulation.[64]

Immunophenotyping

The stages of ALL include early pre-B ALL, common ALL, Pre-B-cell ALL, mature B-cell ALL (Burkitt leukemia), pre-T-cell ALL, and mature T-cell ALL.[65] B-and T-cell lymphoblastic leukemia cells express surface antigens that parallel their respective lineage developments. Precursor B-cell ALL cells typically express CD10, CD19, and CD34 on their surface along, with nuclear terminal deoxynucleotide transferase (TdT), while precursor T-cell ALL cells commonly express CD2, CD3, CD7, CD34, and TdT.[66] In a study by Bayram *et al*. the most frequently detected five antigens were I2, CD10, CD41, CD2, and CD7/CD19 at the time of diagnosis and CD41, I2, CD10, CD19, and CD2 at the time of relapse. Flow cytometric investigations revealed that antigen levels determined at the time of diagnosis increased or decreased by 10% at the time of relapse.[67] CD19 is also expressed on the earliest B-precursor lymphocytes that are malignantly transformed in ALL.

Cytogenetics

Many technical difficulties make it difficult to gain information for chromosomal findings in ALL. Chromosome studies in ALL exhibit poor morphology; chromosomes tend to spread poorly, and appear blurred and fuzzy with indistinct margins, making banding studies challenging or even impossible.[61,68] Williams identified clonal karyotypic abnormalities in 94% to 98% of cases of ALL.[61] The majority of cases of ALL demonstrate an abnormal karyotype, either in chromosome number (ploidy) or as structural changes such as translocations, inversions or deletions. These changes were detected in only half of ALL patients in the first banding studies.[63] Improvements in spreading and banding techniques have resulted in higher rates of detection, and most studies now report chromosomal changes in 60-85% of ALL cases.[69-72] The Third International Workshop on Chromosomes in Leukemia found the majority of cytogenetic changes in cases of B precursor ALL, with only 39% occurring in T-cell ALL.[69,71]

Most studies on karyotypic abnormalities and their clinical significance have been performed in childhood ALL. Adult ALL showed nonrandom chromosomal abnormalities similar to those found in childhood ALL, but their distribution and their biological significance were different. However, in adult ALL the role of cytogenetics in patient management has largely been centered on the presence of the Philadelphia (Ph) chromosome which usually arises from t(9;22)(q34;q11.2) and results in BCR-ABL fusion.[73] Among the several changes, ploidy distribution and recurrent translocation associated with specific morphology and immunophenotype are well-recognized in ALL. Numerical chromosomal abnormalities alone are less common in adult ALL, possibly reflecting a fundamental difference in the pathogenesis between childhood and adult ALL.[74] Among adults, patients with normal karyotype and those with isolated 9p/CDKN2A-CDKN2B deletions had a relatively favorable (standard) prognosis, whereas those with 6q deletions, miscellaneous, and hyperdiploid karyotype had an intermediate prognosis, and patients with t(9;22)/BCR/ABL1, t(4;11)/MLL/AF4, t(1;19)/TCF3/PBX1 constituted the unfavorable prognosis group.[75]

TREATMENT

Leukemia is usually treated with chemotherapy, irradiation, or bone marrow transplantation. Chemotherapy and radiotherapy are generally cytotoxic for rapidly multiplying malignant cells, but also negatively impact the production of normal hemopoietic and secretary cells as these do not differentiate between normal and malignant cells. This side effect often results in immune-suppression and reduced secretions in the body. The systemic sequelae as a result of this medication or radiation can also induce a number of oral and dental complications. The patient with cancer faces an assault on oral health from both the disease and the treatment options. The direct and indirect ill effects to the oral cavity are associated with the development of ulcerative, hemorrhagic, or infectious complications.[76]

ORAL COMPLICATIONS

Various factors increase the potential for developing oral problems in these children. They may include the age of the patient, nutritional status, type of malignancy, pretreatment oral condition, oral care during treatment, and pretreatment neutrophil counts.[76] The oral complications seen in leukemic children can be broadly classified as:[77]

1. Primary complications — Mainly occurring due to the disease itself, that is, resulting from leukemic infiltration in the oral structures such as gingiva and bone. E.g., leukemic gingival enlargement.
2. Secondary complications — These are usually associated with a direct effect of the radiation or chemotherapy, like the ones associated with thrombocytopenia, anemia, and granulocytopenia. These include a tendency to bleeding, susceptibility to infections, and ulcers, etc.
3. Tertiary complications — The tertiary complications are usually due to the complex interplay of therapy itself, its side effect, and a systemic condition arising out of the therapy. They may be ulcerations, mucositis, taste alteration, skin desquamation, candidiasis, gingival bleeding, xerostomia, dysphasia, opportunistic infections, trismus, etc. Sometimes

latent and late effects like some of the vascular lesions, tissue atrophy, permanent taste loss or change, fibrosis, edema, soft tissue necrosis, loss of teeth, salivary flow decrease, carious lesions, osteoradionecrosis, and chondronecrosis are also attributed to tertiary effects.

Mucositis

Mucositis is one of the most common oral problems seen during antileukemic treatment. The patient usually complains of mucosal burning, pain, dry mouth, and discomfort as initial symptoms. Clinically, it manifests as generalized redness or sometimes a pale appearance with an interspersed erythema, scattered ulceration, and/or some bleeding sites. Rarely mucosal swelling is can be seen.[77,78] Even a mild local irritant (like sharp teeth or restoration, calculus, and plaque) may aggravate the mucosal inflammation. Younger patients are more prone to chemotherapy-induced mucositis; may be due to a more rapid epithelial mitotic rate or the presence of more epidermal growth factor receptors. It involves the soft palate, oropharynx, buccal and labial mucosa, floor of the mouth and the ventral and lateral surfaces of the tongue. The pain due to mucositis may lead to difficulty in feeding, hydration and speech, which further may lead to weight loss, anorexia, cachexia, and dehydration.[77,78]

Saliva

Quantitative and qualitative changes in saliva may be seen soon after anticancer therapy. The radiation therapy causes fibrosis, degeneration of salivary acinar cells, and necrosis of salivary glands. Xerostomia is seen due to radiotherapy as well as various chemotherapeutic drugs used during treatment[79,80] leading to increase the incidence of dental caries. There is an increase in viscosity, and organic material of the saliva leading to change is the color from transparent to opaque white or yellow. Decrease in pH and buffering capacity is seen due to alteration in electrolyte levels. The oral flora shows a shift from Gram-positive to Gram-negative bacteria due to low pH. These changes in saliva cause difficulty in chewing, swallowing, speech, taste alteration, dislike for food, and subsequent appetite loss.[77]

Osteoradionecrosis

Osteoradionecrosis is the most severe and serious oral complications of radiotherapy. Radiation damages the endothelial linings of the vessels of the bones resulting in hypocellularity, vasculitis followed by obliterate endarteritis, ischemia, fistula, and sometimes pathological fracture of the bone. The mucosa also becomes thinner with telangiectasia formation in the irradiated area making the bone more susceptible to mechanical injury. There is a decrease in collagen formation and the capacity for wound healing if the bone is subjected to trauma, e.g., tooth extraction.[81]

Opportunistic Infections

Candidiasis is the most common opportunistic infections seen in children with leukemia. Candida species adhere to the epithelial surface via extracellular polymeric materials and further penetrates by liberation of enzymes.[81] The presentation of candidiasis may vary from soft white adherent patches (pseudomembraous candidiasis) to erythematous painful eroded areas(erythematous form) on the oral mucosa. It has been observed clinically that acute pseudomembraous candidiasis progresses to erythematous candidiasis. Children suffer from increased risk of dissemination of Candida infection, which may be life-threatening.[82]

Herpes simplex is clinically manifested as multiple ulcers at corners of the mouth, lips, palate, and gingiva. An erythema may also be seen around the ulcerative lesions. Varicella zoster is seen as multiple blisters, which show a protracted course. Other infections seen in these patients include tuberculosis and pneumonia.[83]

Hemorrhage

Hemorrhage seen in the leukemic patient may range from minor bleed from inflamed gingiva to ecchymosis, hematoma, or hemorrhage depending upon the severity of thrombocytopenia, oral hygiene, and contributing factors like sharp tooth of denture, etc. Petechiae and ecchymosis are commonly found on gingiva, buccal mucosa, tongue, floor of the mouth, and hard and soft palate. Spontaneous mucosal petechiae and gingival bleeding can occur when the platelet level drops below 20,000 cells/mm^3. Spontaneous bleeding or bleeding from traumatic brushing may be seen commonly from gingiva in patients receiving chemotherapy.[83,84]

Dysguesia/Taste alteration

Salivary changes and damage to the gustatory buds due to radiation leads to taste alteration. There is 50% reduction in the perception of bitter and sour tastes. Venous taste phenomenon caused due to diffusion of chemotherapeutic drugs into the oral cavity adds on to bad taste. Taste loss is often transitional and partial or total recovery is seen between 2 and 112 months postmyelosuppressive therapy.[85]

Trismus

Trismus is a consequence of edema, cellular destruction, and muscular fibrosis or degeneration caused by chemotherapeutic agents and radiation. Limited mouth opening may also lead to an inadequate oral hygiene, further hampering the health of the oral cavity.[83]

Dental caries

Alterations in salivary gland, tendency to eat a soft diet, changes in the oral microflora, and inability to

maintain an oral hygiene causes an increase in dental caries experience in the leukemic patient. Dens *et al*.,[86] observed a significantly higher caries experience in children receiving chemotherapy.

Damage to developing orofacial structures

Exposure of developing tooth germ during the formative years (before the age of 9 years) to chemotherapeutic agents or radiotherapy can damage the ameloblasts and odontoblasts, causing arrested tooth formation or hypomineralization or hypomaturation of enamel, or short, thin, tapered roots. Incomplete development of the jaws can also be seen. The younger the child, the greater is the risk for craniofacial and developmental abnormalities.[87]

PROGNOSIS

Dramatic medical advancements in the treatment of ALL over the past three decades have changed it from a universally fatal to an almost curable disease in 85% of cases. Pediatric oncologists have become more successful in treating ALL as much of the clinical research efforts have focused on categorizing the patients into lower risk group (needing less intense therapy with much less side effects and toxicities) and patient with higher risk of treatment failure (targeted for more aggressive therapies)[88] based on known prognostic features. In the risk classification of ALL, not only cytogenetic alterations, but also many other factors are taken into account. These include, for example, WBC count at diagnosis, age, response to primary therapy, and the phenotype of the blasts (precursor-B cell/immature B cell/T cell).[89] The groups of patients formed according to the existing criteria, however, quite heterogeneous as regards the outcome of the patients, leading to excessive treatment of some patients and failure of treatment in others.

The cytogenetic abnormalities confer important prognostic information in ALL was first reported by Secker-Walker *et al*. in 1982 in a series of childhood ALL.[90] Complete remission rates, remission durations, as well as disease-free-survivals, were significantly affected by the karyotypic abnormalities.[69] Cytogenetic studies in childhood ALL have associated a better prognosis with the hyperdiploid karyotype and a worse prognosis with a balanced translocation.[90,91] The correlation of the karyotype in ALL with other recognized prognostic factor is an independent prognostic in childhood[92] as well as in adult patients.[93] The clinical outcome of patients with hyperdiploidy varies in different series, being more favorable in children than in adults, where a poor outcome has been repeatedly reported.[70,93]

The survival rate for children younger than 15 years of age reaches about 75%, but, despite the significant improvement of outcome, still roughly 25% of patients suffer from a relapse.[94] Even if the management of relapse remains largely controversial, an increasing use of high-dose chemotherapy and stem cell transplantation is adopted in most cases. With the need to stratify patients in risk groups and to provide risk-adapted therapy, treatment requires high levels of organization, expertise, and knowledge.

Multiple inter-related factors are responsible for the poorer outlook of childhood cancer in India. Limited financial resources, lack of awareness of the meaning of symptoms, and difficulty in accessing healthcare contribute to advanced stage presentation.[95] Such a delay in presentation, along with unfavorable biology (e.g., as seen in ALL), leads to a need for more intense treatment, resulting in higher treatment-related morbidity and mortality.[96,97] Treatment refusal or abandonment, besides treatment-related death, is a frequent unwanted outcome.[98] A higher 5-year survival seen in those treated at specialist cancer centers and among those who complete their treatment reinforces the importance of centralization of treatment and compliance.[99] Recently, twinning programs, which foster interactions between public hospitals in developing countries and established cancer treatment centers elsewhere, have been seen to reduce abandonment and improve survival elsewhere in the world.[100-104] Similar strategies could be applied here. Clinical trials started by the Indian Cooperative Oncology Network (ICON, www.oncologyindia.org) and adoption of the MCP841 protocol for ALL in major Indian centers have been steps in the right direction for improving childhood cancer outcome.[97]

CONCLUSION

In India, child health is a priority health issue, and we are progressing toward reducing infection related childhood deaths. But childhood cancer is not yet a major area of focus, and it is not acceptable to ignore these children as they have an increasing likelihood of cure with appropriate treatment.

REFERENCES

1. Ferretti GA, Ash RC, Brown AT, Largent BM, Kaplan A, Lillich TT. Chlorhexidine for prophylaxis against oral infections and associated complications in patients receiving bone marrow transplants. J Am Dent Assoc 1987;114:461-7.
2. Genc A, Atalay T, Gedikoglu G, Zulfikar B, Kullu S. Leukemic children: Clinical and histopathological gingival lesions. J Clin Pediatr Dent 1998;22:253-6.
3. Subramaniam P, Babu KL, Nagarathna J. Oral manifestations in acute lymphoblastic leukemic children under chemotherapy. J Clin Pediatr Dent 2008;32:319-24.
4. Meadors GF. Epidemiology of leukemia. Public Health Rep 1956;71:103-8.
5. Forkner CE. Leukemia and Allied Disorders. New York: Macmillan Co.; 1938. p. 333.

6. Ries LA, Percy CL, Bunin GR. SEER Pediatric monograph. In: Ries L, Smith M, Gurney JG, *et al*., editors. Cancer incidence and survival among children and adolescents: United States SEER program 1975-1999 [NIH (Pub. No. 99-4649]. Bethesda (MD): National Cancer Institute, SEER program; 1999 (Available from: http://www.seer.cancer.gov).
7. Stiller C, editor. Childhood Cancer in Britain: Incidence Survival, Mortality. Oxford: Oxford University Press; 2007.
8. Ribera JM, Oriol A. Acute lymphoblastic leukemia in adolescents and young adults. Hematol Oncol Clin North Am 2009;23:1033-42, vi.
9. Amare P, Gladstone B, Varghese C, Pai S, Advani S. Clinical significance of cytogenetic findings at diagnosis and in remission in childhood and adult acute lymphoblastic leukemia: Experience from India. Cancer Genet Cytogenet 1999;110:44-53.
10. Magrath I, Shanta V, Advani S, Adde M, Arya LS, Banavali S, *et al.* Treatment of acute lymphoblastic leukaemia in countries with limited resources; lessons from use of a single protocol in India over a twenty year period [corrected]. Eur J Cancer 2005;41:1570-83.
11. Rajalekshmy KR, Abitha AR, Pramila R, Gnanasagar T, Maitreyan V, Shanta V. Immunophenotyping of acute lymphoblastic leukaemia in Madras, India. Leuk Res 1994;18:183-90.
12. Siraj AK, Kamat S, Gutiérrez MI, Banavali S, Timpson G, Sazawal S, *et al*. Frequencies of the major subgroups of precursor B-cell acute lymphoblastic leukemia in Indian children differ from the West. Leukemia 2003;17:1192-3.
13. Escalon EA. Acute lymhocytic leukemia in childhood. Int Pediatr 1999;4:83-9.
14. Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, *et al*. Outcomes for children and adolescents with cancer: Challenges for the twenty-first century. J Clin Oncol 2010;28:2625-34.
15. Lu Q, Wright DD, Kamps MP. Fusion with E2A converts the Pbx1 homeodomain protein into a constitutive transcriptional activator in human leukemias carrying the t (1;19) translocation. Mol Cell Biol 1994;14:3938-48.
16. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, *et al.* Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: A report from the children's oncology group. J Clin Oncol 2012;30:1663-9.
17. Baccichet A, Benachenhou N, Couture F, Leclerc JM, Sinnett D. Microsatellite instability in childhood T cell acute lymphoblastic leukemia. Leukemia 1997;11:797-802.
18. Moorman AV, Richards SM, Martineau M, Cheung KL, Robinson HM, Jalali GR, *et al*. Outcome heterogeneity in childhood high-hyperdiploid acute lymphoblastic leukemia. Blood 2003;102:2756-62.
19. Knudson AG. Chasing the cancer demon. Annu Rev Genet 2000;34:1-19.
20. Besson C, Gonin C, Brebion A, Delaunay C, Panelatti G, Plumelle Y. Incidence of hematological malignancies in Martinique, French West Indies, overrepresentation of multiple myeloma and adult T cell leukemia/lymphoma. Leukemia 2001;15:828-31.
21. Yanada M, Jinnai I, Takeuchi J, Ueda T, Miyawaki S, Tsuzuki M, *et al.* Clinical features and outcome of T-lineage acute lymphoblastic leukemia in adults: A low initial white blood cell count, as well as a high count predict decreased survival rates. Leuk Res 2007;31:907-14.
22. Rathee R, Kamal N, Kumar A, Vashist M, Yadav R. Dermatoglyphic Patterns of Acute Leukemia Patients. Int Res J Biological Sci 2014;3:90-93.
23. Taub JW, Konrad MA, Ge Y, Naber JM, Scott JS, Matherly LH, *et al.* High frequency of leukemic clones in newborn screening blood samples of children with B-precursor acute lymphoblastic leukemia. Blood 2002;99:2992-6.
24. Greaves MF, Maia AT, Wiemels JL, Ford AM. Leukemia in twins: Lessons in natural history. Blood 2003;102:2321-33.
25. Greaves M. In utero origins of childhood leukaemia. Early Hum Dev 2005;81:123-9.
26. Modak H, Kulkarni SS, Kadakol GS, Hiremath SV, Patil BR, Hallikeri U, *et al.* Prevalence and risk of leukemia in the multi-ethnic population of North Karnataka. Asian Pac J Cancer Prev 2011;12:671-5.
27. Clarke CA, Edwards JW, Haddock DR, Howel-Evans AW, Mcconnell RB, Sheppard PM. ABO blood groups and secretor character in duodenal ulcer; population and sibship studies. Br Med J 1956;2:725-31.
28. Roberts JA. Blood groups and susceptibility to disease: A review. Br J Prev Soc Med 1957;11:107-25.
29. Macmahon B, Folusiak JC. Leukemia and ABO blood group. Am J Hum Genet 1958;10:287-93.
30. Jackson N, Menon BS, Zarina W, Zawawi N, Naing NN. Why is acute leukemia more common in males? A possible sex-determined risk linked to the ABO blood group genes. Ann Hematol 1999;78:233-6.
31. Kumar A, Rathee R, Vashist M, Neelkamal S, Singh S, Gupta S. Acute lymphocytic leukemia: An epidemiological and hematological study from Haryana. Biosci Biotechnol Res Asia 2012;9:813-7.
32. Ramot B, Magrath I. Hypothesis: The environment is a major determinant of the immunological sub-type of lymphoma and acute lymphoblastic leukaemia in children. Br J Haematol 1982;50:183-9.
33. Varghese PR, Elayidom NB, Joseph CD, Kumar S. Epidemiological observations on leukemia in Kerala (A study of 1016 cases over three years). Indian J Haematol 1984;2:15-17.
34. Advani SH, Jussawalla DJ, Rao DN, Gangadharan P, Shetty PA. A study of 1126 leukaemia cases — Epidemiologic and end result analysis. Indian J Cancer 1979;16:8-17.
35. Pradhan PK, Tiwari SK, Dabke AT, Agarwal S. Pattern of leukaemia in Raipur (Madhya Pradesh) — An analysis of 162 cases. Indian J Cancer 1982;19:20-3.
36. Chatterjea JB, Ghose S, Ray RN. Incidence of leukaemia. (An analysis of 544 cases studied in Calcutta). J Assoc Physicians India 1962;10:673-6.
37. Rani S, Beohar PC, Mohanty TK, Mathur MD. Leukaemic pattern in Delhi — A ten year study of 490 cases. Indian J Cancer 1982;19:81-6.
38. Hanson MR, Mulvihill JJ. Epidemiology of child-blood cancer. In: Levine AS, editor. Cancer in the Young. NewYork: Masson; 1980. p. 3-12.
39. Draper GJ, Kroll ME, Stiller CA. Childhood cancer. Cancer Surv 1994;19-20:493-517.
40. Gurney JG, Davis S, Severson RK, Fang JY, Ross JA, Robison LL. Trends in cancer incidence among children in the U.S. Cancer 1996;78:532-41.
41. Holmes L Jr, Hossain J, Desvignes-Kendrick M, Opara F. Sex variability in pediatric leukemia survival: Large cohort evidence. ISRN Oncol 2012;2012:439070.
42. Miller RW. Special susceptibility of the child to certain radiation-induced cancers. Environ Health Perspect 1995;103 Suppl 6:41-4.
43. Schmitz-Feuerhake I, Dannheim B, Heimers A, Oberheitmann B, Schröder H, Ziggel H. Leukemia in the proximity of a German boiling-water nuclear reactor: Evidence of population exposure by chromosome studies and environmental radioactivity. Environ Health Perspect 1997;105 Suppl 6:1499-504.
44. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. Br J Radiol 1997;70:130-9.
45. Infante-Rivard C, Fortier I, Olson E. Markers of infection, breast-feeding and childhood acute lymphoblastic leukaemia. Br J Cancer 2000;83:1559-64.
46. Bartley K, Metayer C, Selvin S, Ducore J, Buffler P. Diagnostic X-rays and risk of childhood leukaemia. Int J Epidemiol 2010;39:1628-37.
47. Shu XO, Linet MS, Steinbuch M, Wen WQ, Buckley JD, Neglia JP, *et al.* Breast-feeding and risk of childhood acute leukemia. J Natl Cancer Inst 1999;91:1765-72.
48. Feychting M, Schulgen G, Olsen JH, Ahlbom A. Magnetic fields and childhood cancer: A pooled analysis of two Scandinavian studies. Eur J Cancer 1995;31A:2035-9.
49. Wertheimer N, Savitz DA, Leeper E. Childhood cancer in relation to indicators of magnetic fields from ground current sources. Bioelectromagnetics 1995;16:86-96.
50. Toledano SR, Lange BJ. Ataxia-telangiectasia and acute lymphoblastic leukemia. Cancer 1980;45:1675-8.
51. Shaw MP, Eden OB, Grace E, Ellis PM. Acute lymphoblastic leukemia and Klinefelter's syndrome. Pediatr Hematol Oncol 1992;9:81-5.
52. Mertens AC, Wen W, Davies SM, Steinbuch M, Buckley JD, Potter JD, *et al.* Congenital abnormalities in children with acute leukemia: A report from the Children's Cancer Group. J Pediatr 1998;133:617-23.
53. Chessells JM, Harrison G, Richards SM, Bailey CC, Hill FG, Gibson BE, *et al*. Down's syndrome and acute lymphoblastic leukaemia: Clinical features and response to treatment. Arch Dis Child 2001;85:321-5.

54. Greaves MF, Colman SM, Beard ME, Bradstock K, Cabrera ME, Chen PM, *et al.* Geographical distribution of acute lymphoblastic leukaemia subtypes: Second report of the collaborative group study. Leukemia 1993;7:27-34.
55. Greaves MF. Aetiology of acute leukaemia. Lancet 1997;349:344-9.
56. Kinlen LJ. Infection and childhood leukemia. Cancer Causes Control 1998;9:237-9.
57. Jourdan-Da Silva N, Perel Y, Méchinaud F, Plouvier E, Gandemer V, Lutz P, *et al.* Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. Br J Cancer 2004;90:139-45.
58. Roman E, Simpson J, Ansell P, Kinsey S, Mitchell CD, McKinney PA, *et al.* Childhood acute lymphoblastic leukemia and infections in the first year of life: A report from the United Kingdom Childhood Cancer Study. Am J Epidemiol 2007;165:496-504.
59. Lombardi L, Newcomb EW, Dalla-Favera R. Pathogenesis of Burkitt lymphoma: Expression of an activated c-myc oncogene causes the tumorigenic conversion of EBV-infected human B lymphoblasts. Cell 1987;49:161-70.
60. Gessain A, Renaud M, Guy T. Genetic variability and molecular epidemiology of human and simian T-cell leukemia/lymphoma virus type I. Mel Infect 1996;13:132-45.
61. Williams CK. Some biological and epidemiological characteristics of human leukaemia in Africans. IARC Sci Publ 1984;687-712.
62. Yunis JJ. Recurrent chromosomal defects are found in most patients with acute nonlymphocytic leukemia. Cancer Genet Cytogenet 1984;11:125-37.
63. Heim S, Békàssy AN, Garwicz S, Heldrup J, Kristoffersson U, Mandahl N, *et al.* Bone marrow karyotypes in 94 children with acute leukemia. Eur J Haematol 1990;44:227-33.
64. Neville B, Damm D, Allen C, Bouquot J. Oral and Maxillofacial Pathology. 3rd ed. Philadelphia: Saunders Elsevier; 2009.
65. Bene MC, Castoldi G, Knapp W, Ludwig WD, Matutes E, Orfao A, *et al.* Proposals for the immunological classification of acute leukemias. European Group for the Immunological Characterization of Leukemias (EGIL). Leukemia 1995;9:1783-6.
66. Pui CH, Jeha S. New therapeutic strategies for the treatment of acute lymphoblastic leukaemia. Nat Rev Drug Discov 2007;6:149-65.
67. Bayram I, Erbey F, Kömür M, Kibar F, Tanyeli A. Flow cytometry results at diagnosis and relapse in childhood acute lymphoblastic leukemia. Asian Pac J Cancer Prev 2010;11:1321-4.
68. Mittelman F. The 3rd international workshop on chromosomes in leukemia. Lund, Sweden, July 21-25, 1980. Introduction. Cancer Genet Cytogenet 1981;4:96-8.
69. Heim S, Békàssy AN, Garwicz S, Heldrup J, Kristoffersson U, Mandahl N, *et al.* Bone marrow karyotypes in 94 children with acute leukemia. Eur J Haematol 1990;44:227-33.
70. Third International Workshop on Chromosomes in Leukemia (TIWCL). Chromosomal abnormalities and their clinical significance in acute lymphoblastic leukemia. Cancer Res 1983;43:868-70.
71. Fenaux P, Lai JL, Morel P, Nelken B, Taboureau O, Deminatti M, *et al.* Cytogenetics and their prognostic value in childhood and adult acute lymphoblastic leukemia (ALL) excluding L3. Hematol Oncol 1989;7:307-17.
72. Rieder H, Ludwig WD, Gassmann W, Thiel E, Löffler H, Hoelzer D, *et al.* Chromosomal abnormalities in adult acute lymphoblastic leukemia: Results of the German ALL/AUL study group. Recent Results Cancer Res 1993;131:133-48.
73. Secker-Walker LM, Prentice HG, Durrant J, Richards S, Hall E, Harrison G. Cytogenetics adds independent prognostic information in adults with acute lymphoblastic leukaemia on MRC trial UKALL XA. MRC Adult Leukaemia Working Party. Br J Haematol 1997;96:601-10.
74. Faderl S, Garcia-Manero G, Thomas DA, Kantarjian HM. Philadelphia chromosome-positive acute lymphoblastic leukemia- current concepts and future perspectives. Rev Clin Exp Hematol 2002;6:142-60.
75. Charrin C, Thomas X, Ffrench M, Le QH, Andrieux J, Mozziconacci MJ, *et al.* A report from the LALA-94 and LALA-SA groups on hypodiploidy with 30 to 39 chromosomes and near-triploidy: 2 possible expressions of a sole entity conferring poor prognosis in adult acute lymphoblastic leukemia (ALL). Blood 2004;104:2444-51.
76. Mancini M, Scappaticci D, Cimino G, Nanni M, Derme V, Elia L, *et al.* A comprehensive genetic classification of adult acute lymphoblastic leukemia (ALL): Analysis of the GIMEMA 0496 protocol. Blood 2005;105:3434-41.
77. Ilgenli T, Oren H, Uysal K. The acute effects of chemotherapy on the oral cavity. Prevention and management. Turk J Cancer 2001;31:93-105.
78. Emidio TC, Maeda YC, Caldo-Teixeira AS, Puppin-Rontani RM. Oral manifestations of leukemia and antineoplastic treatment: A literature review (part II). Braz J Health 2010;1:136-49.
79. Ps SK, Balan A, Sankar A, Bose T. Radiation induced oral mucositis. Indian J Palliat Care 2009;15:95-102.
80. Gupta A, Epstein JB, Sroussi H. Hyposalivation in elderly patients. J Can Dent Assoc 2006;72:841-6.
81. Grimaldi N, Sarmento V, Provedel L, Almeida D, Cunha S. Dental care in prevention and treatment of osteoradionecrosis: Literature review. Rev Bras Cancerol 2005;51:319-24.
82. Scully C. Oral and Maxillofacial Medicine: The Basis of Diagnosis and Treatment. 4th ed. London: Elsevier Science Limited; 2004. p. 252-68.
83. Greenberg MS, Glick M, Skip JA. Burket's Oral Medicine. 11th ed. Hamilton: BC Decker Inc.; 2008. p. 79-84.
84. Mathur VP, Dhillon JK, Kalra G. Oral health in children with leukemia. Indian J Palliat Care 2012;18:12-8.
85. Wright JR, McKenzie M, DeAngelis C, Foroudi F, Paul N, Rajaraman M, *et al.* Radiation induced mucositis: Co-ordinating a research agenda. Clin Oncol (R Coll Radiol) 2003;15:473-7.
86. Pavlatos J, Gilliam KK. Oral care protocols for patients undergoing cancer therapy. Gen Dent 2008;56:464-78.
87. Dens F, Boute P, Otten J, Vinckier F, Declerck D. Dental caries, gingival health, and oral hygiene of long term survivors of paediatric malignant diseases. Arch Dis Child 1995;72:129-32.
88. Xavier AM, Hegde AM. Preventive protocols and oral management in childhood leukemia: The pediatric specialist's role. Asian Pac J Cancer Prev 2010;11:39-43.
89. Weinstein HJ. The role of prognostic features in the treatment of childhood acute lymphoblastic leukemia. Hematol Oncol Clin North Am 2009;23:1033-42.
90. Gustafsson G, Schmiegelow K, Forestier E, Clausen N, Glomstein A, Jonmundsson G, *et al.* Improving outcome through two decades in childhood ALL in the Nordic countries: The impact of high-dose methotrexate in the reduction of CNS irradiation. Nordic Society of Pediatric Haematology and Oncology (NOPHO). Leukemia 2000;14:2267-75.
91. Secker-Walker LM, Swansbury GJ, Hardisty RM, Sallan SE, Garson OM, Sakurai M, *et al.* Cytogenetics of acute lymphoblastic leukaemia in children as a factor in the prediction of long-term survival. Br J Haematol 1982;52:389-99.
92. Williams DL, Tsiatis A, Brodeur GM, Look AT, Melvin SL, Bowman WP, *et al.* Prognostic importance of chromosome number in 136 untreated children with acute lymphoblastic leukemia. Blood 1982;60:864-71.
93. Groupe Français de Cytogénétique Hématologique (GFCH). Cytogenetic abnormalities in adult acute lymphoblastic leukemia: Correlations with hematologic findings and outcome. A collaborative study of the Groupe Français de Cytogénétique Hématologique. Blood 1996;87:3135-8.
94. Wetzler M, Dodge RK, Mrózek K, Carroll AJ, Tantravahi R, Block AW, *et al.* Prospective karyotype analysis in adult acute lymphoblastic leukemia: The cancer and leukemia Group B experience. Blood 1999;93:3983-93.
95. Moorman AV, Richards SM, Robinson HM, Strefford JC, Gibson BE, Kinsey SE, *et al.* Prognosis of children with acute lymphoblastic leukemia (ALL) and intrachromosomal amplification of chromosome 21 (iAMP21). Blood 2007;109:2327-30.
96. Arora RS, Eden TO, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer 2009;46:264-73.
97. Barr R, Riberio R, Agarwal B, Masera G, Hesseling P, Magrath I. Pediatric oncology in countries with limited resources. In: Pizzo PA, Poplack DG, editors. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2006. p. 1605-17.
98. Arora B, Kurkure P, Parikh P. Childhood cancers: Perspectives in India. J Indian Med Assoc 2005;103:479-82.

99. Arora RS, Eden T, Pizer B. The problem of treatment abandonment in children from developing countries with cancer. Pediatr Blood Cancer 2007;49:941-6.
100. Swaminathan R, Rama R, Shanta V. Childhood cancers in Chennai, India, 1990-2001: Incidence and survival. Int J Cancer 2008;122:2607-11.
101. Harif M, Barsaoui S, Benchekroun S, Bouhas R, Doumbé P, Khattab M, *et al.* Treatment of B-cell lymphoma with LMB modified protocols in Africa: Report of the French-African Pediatric Oncology Group (GFAOP). Pediatr Blood Cancer 2008;50:1138-42.
102. Howard SC, Pedrosa M, Lins M, Pedrosa A, Pui CH, Ribeiro RC, *et al.* Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. JAMA 2004;291:2471-5.
103. Qaddoumi I, Musharbash A, Elayyan M, Mansour A, Al-Hussaini M, Drake J, *et al.* Closing the survival gap: Implementation of medulloblastoma protocols in a low-income country through a twinning program. Int J Cancer 2008;122:1203-6.
104. Rivera GK, Quintana J, Villarroel M, Santana VM, Rodriguez-Galindo C, Neel MD, *et al.* Transfer of complex frontline anticancer therapy to a developing country: The St. Jude osteosarcoma experience in Chile. Pediatr Blood Cancer 2008;50:1143-6.

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