Oral manifestations of leukemia and antineoplastic treatment – a literature review (part I)

Abstract
Cancer is one of the diseases that have been most discussed and researched, due to high incidence and their potential for malignancy, especially if not diagnosed early. Leukemia is the most common malignant disease of childhood and it is characterized by uncontrolled leukocyte production in immature form (blasts). Traditional methods of antineoplastic treatment include chemotherapy, radiotherapy, surgery, as well as the use of non-conventional medicine which can also be observed. However, normal cells such as those of oral and gastrointestinal mucosa, bone marrow, and skin also have similar degree of mitotic activity and are especially likely to show neoplastic agent side effects. The effects of antineoplastic therapy may be reversible and/or progressive and irreversible. In addition to that, these effects can cause an impact on the patient’s treatment course, on quality of life, and morbidity and mortality. This literature review aims to clarify the characteristics of leukemia, showing not only the symptoms, but also treatment alternatives and its effects.

Key-words: leukemia; oncology; neoplastic agents.

Resumo
O câncer é uma das enfermidades que mais vem sendo discutida e pesquisada na atualidade, tendo em vista sua alta incidência e seu potencial de malignidade, especialmente se não diagnosticada precocemente. A leucemia é a doença maligna mais comum da infância, e caracteriza-se pela produção descontrolada de leucócitos na forma imatura (blastos). Métodos tradicionais de tratamento antineoplásico incluem quimioterapia, radioterapia, cirurgia, assim como a medicina não-convencional também pode ser observada. Entretanto, células normais como às da mucosa gastro-intestinal, medula óssea, e pele têm um grau de atividade mitótica e demonstram-se suscetíveis aos efeitos dos agentes antineoplásicos. Os efeitos da terapia antineoplásica podem ser reversíveis ou progressivos e irreversíveis. E mais, isso produz um impacto no curso do tratamento, na qualidade de vida, e na morbidade e mortalidade. Essa revisão da literatura tem o objetivo e...
esclarecer características da leucemia, apresentando não somente os sintomas, mas também as alternativas de tratamento e seus efeitos.

Palavras-chave: leucemia; oncologia; agentes neoplásicos.

Introduction

In Brazil, statistics on childhood cancer have been little examined in the national literature, despite the existence of data sources, such as the Mortality Information System of the Ministry of Health and the population-based cancer registry data existing in Brazil\textsuperscript{1}.

According to estimates of the National Cancer Institute, 3,105 children died of cancer in 2005. In 2007, the Unified Health System (\textit{Sistema Único de Saúde - SUS}) registered 52,392 hospital admissions for children and adolescents with cancer, between the ages of 5 and 19 years. Excluding external causes, pediatric cancer is the leading cause of death by disease among children over 4 years of age. Each year, 160 thousand children and adolescents worldwide are diagnosed with cancer and an estimated 90 thousand die of the disease\textsuperscript{2}.

Considering the age group below 15 years, of every 10 to 15 cases of cancer, in Brazil, four are acute lymphoblastic leukemia\textsuperscript{3,4}, which shows that leukemia is the most frequent diagnosis in children\textsuperscript{1,2,4,5}.

Leukemia is the leading cause of death among children, accounting for 39\% of deaths in Europe and 50\% in the Americas, Oceania and Asia. The decline observed in several countries in the childhood cancer mortality rates for children under 15 years appears to be due in large part to the increased probability of survival for most cases of childhood tumors, i.e., the increase in the percentage of children living with cancer after a period of time is due to earlier diagnosis and greater success in therapeutic interventions (radiotherapy, chemotherapy, surgery, bone marrow transplantation). Recent advances in the use of chemotherapeutic drugs and the use of combined regimens of drugs allowed the survival of children with cancer, particularly those diagnosed with hematologic malignancies\textsuperscript{1}.

In almost all groups diagnosed with cancer, the chances of survival have increased. However, there may be a wide variation between the chances of survival for patients diagnosed with different tumors. Such variations depend on the natural history of the disease, the affected organ, and the varied responses to anticancer therapy. Pediatric neoplasia is usually a fatal disease when not properly treated or in a timely fashion\textsuperscript{1}.

Although, in many countries, there has been an increased cancer incidence in children under 15 years and the prognosis for many childhood tumors is still lower than desired, the survival of children with cancer is better today. The increase in survival rates has
become more striking particularly for some histological types

The first part of this literature review aims to clarify the characteristics of leukemia, the primary malignant disease of childhood, showing not only the symptoms, but also treatment alternatives and their effects.

**Literature Review**

Leukemia is characterized by disorderly independent overproduction of immature white blood cells. Any tissue or organ can be affected, depending on the infiltration by leukemic cells from the blood, namely the clinical manifestations of this disease can occur in all organs and tissues irrigated and nourished by the blood including the oral tissues. Anaemia (number of red blood cells below normal), leukocytopenia (number of white cells below normal) and thrombocytopenia (number of platelets below normal) are also observed.

Its etiology is still unknown, but may be related to exposure to viral infection, ionizing radiation, other types of electromagnetic radiation, chemical exposure and cytogenetic changes.

Leukemia can be acute or chronic and may be related to granulocytes, monocytes or lymphocytes, being classified as myeloid, lymphoid (or lymphocytic), and monocytic, respectively. The diagnosis is carried out by the identification of abnormal hematopoietic cells in the peripheral blood and bone marrow. And its characterization is performed by cytochemical marking, immunophenotyping and cytogenetic analysis of cromossomic abnormalities.

Leukemia prognosis improved significantly in recent decades, and currently, the chance of survival for a patient with acute lymphoblastic leukemia (ALL), the most common type of leukemia in childhood, is 77%.

The most common clinical manifestations are: 1) fatigue: due to anemia. Low hemoglobin count reduces yield due to efficiency in oxygen capture, thus easily causing fatigue; 2) fever: low and constant, which generally is not reduced with medicines prescribed by pediatricians. Fever indicates infection or hypermetabolic state caused by a rapid growth or destruction of the leukemic tissue, besides depressed immune system. Leukocyte count is generally less than 10,000 cells/mm³ (the normal cell count is 6,000/mm³), with 60% to 100% of immature lymphocyte cells; 3) malaise, anorexia, irritability; 4) diffuse infection of organs and tissues: lymphadenopathy and splenomegaly result from cell infiltration into those organs; 5) infiltration in subperiostic tissue which can involve the meninges with manifestations in the central nervous system, provoking headache, vomiting, cranial nerve paralysis, loss of consciousness, and even coma.

Traditional methods of antineoplastic treatment include chemotherapy, radiotherapy, surgery, as well as the use of non-
conventional medicine which can also be observed\textsuperscript{19,20}.

The treatment to be established depends on the location, malignancy degree of the clinical staging of the tumor, and the individual’s health condition\textsuperscript{22,23}.

The main function of antineoplastic therapy is the destruction of malignant cells, preferably when they are at the stage of mitosis. However, normal cells such as those of oral and gastrointestinal mucosa, bone marrow, and skin also have similar degree of mitotic activity and are especially likely to show neoplastic agent side effects\textsuperscript{8,16,17,18,22,25-27}.

The effects of antineoplastic therapy may be reversible (chemotherapy) or progressive and irreversible (radiotherapy) and depends on factors related to the patient, duration and volume of treatment, distribution and dose of concomitant use of other therapies\textsuperscript{8}. In addition, it often leads to oral complications such as mucositis, gingival bleeding, xerostomia, candidiasis, loss of taste, trismus, and systemic side effects (leukopenia, anemia, and plateletopenia)\textsuperscript{8,16,28,29}.

**Chemotherapy**

Chemotherapy can be classified according to its purposes into four types: 1) curative: used to control the tumor; 2) supporting: in combination with surgery to reduce the incidence of metastasis at distance; 3) previous: complementary treatment to surgery and/or radiotherapy, in order to obtain a partial reduction of the tumor; and 4) palliative: non-curative, aims to improve survival of patients\textsuperscript{8,22}.

Chemotherapy occurs in three therapeutic stages: 1) induction - administration of high doses of antineoplastic agents, aiming to promote the early death of malignant cells; the response to therapy occurs between 4-6 weeks, reflecting the prognosis of disease; 2) consolidation or intensification - designed to kill residual neoplastic cells, which can persist in significant numbers after induction; this phase is short term, but in very intense concentration or combination of drugs used; and 3) maintenance - complete remission of the disease is expected, which is demonstrated through exams\textsuperscript{17}.

Intensive chemotherapy whether or not associated with radiotherapy is the treatment used in most cases\textsuperscript{30}. In severe cases, the surgical procedure in combination with chemotherapy and/or radiotherapy is used\textsuperscript{8,16,22,25}.

Oral manifestations resulting from chemotherapy are developed after several days of treatment\textsuperscript{31} and vary depending on the drug to which the patient is submitted as well as on its own organism\textsuperscript{4,10}.

**Radiotherapy**

Radiotherapy alone or combined with surgery, with chemotherapy or with both is an effective treatment modality for many malignancies and survival rates are high in cancer treatment\textsuperscript{8}.
This type of therapy uses ionizing radiation aiming at destroying the neoplastic cells, seeking a reduction or disappearance of the malignant tumor\(^8\).

Unfortunately, the adjacent healthy cells are also affected by damaging the cell nuclear material, essential for cell breeding and maintaining its stability. Intranuclear structures and tissues with a greater capacity for renewal are the most affected\(^{25}\). The extent and severity of tissue lesions will depend on the total dose of radiotherapy, the biological effective dose, the size of the field irradiated, the number and intervals between sessions, dose fractionation and surgical and/or traumatic aggression to the irradiated tissue\(^{23,32,33}\).

Radiotherapy treatment options are divided into two modalities: teleradiotherapy (radiation from a distant source) and brachytherapy (implants through intraluminal or endocavity applicators and in direct contact with radioisotopes)\(^{34}\). The choice of the treatment depends on the type of cancer and the depth of tumor\(^{23,35}\).

Although teleradiotherapy is the most frequently used, its side effects affect particularly the oral cavity\(^{23,34,36}\). The nature of oral complications depends on factors such as location and type of cancer, patient’s age, dose of radiation, prophylaxis employed against the oral microbial pathogens, pre-existing condition and oral status during treatment\(^{24}\).

With regard to the dose used, the Gray (Gy) is the unit of absorbed dose (1 Gy = 100 rad)\(^8\), the literature shows that rates between 22.2 to 54 Gy damage the parenchyma of the salivary glands, causing fibrosis and decrease of saliva secretion. This effect can cause permanent xerostomia\(^{14,15,27}\). Severe alterations can be observed with the use of 50-60 Gy, causing dental alterations in 90% to 100% of cases\(^8\).

The main side effects of radiotherapy are: xerostomia, trismus, radiation caries, candidiasis, osteoradionecrosis, mucosal hyperpigmentations, and mucositis\(^{23,34,37}\) and can be accentuated by various factors, such as dysfunction of the salivary glands, compromising the barrier function, lubrication and antimicrobial action of saliva; mucosal trauma/irritation; infection caused by the native oral microbiota (particularly opportunistic oral microorganisms); acquired pathogens, as well as reactivation of other infections\(^{14,15}\).

When it comes to child patients, the late local effects lead to change in odontogenesis (enamel hypoplasia, dental development stop, anodontia, microdontia), and rhizogenesis. These effects are more pronounced when the two therapies (chemotherapy and radiotherapy) are combined\(^{8,31,38}\).

**Surgical treatment**

The surgical treatment of cancer has the following main objectives: resection of the tumor mass and other tissues involved, such
as the lymph nodes, and removal of endocrine organs, which can modify the spread of the disease\textsuperscript{11,26}.

**Non-conventional medicine**

Non-conventional medical practice includes prevention, diagnosis and treatment outside the official medicine field. It can be divided into two types: complementary medicine and alternative medicine. Complementary medicine is used along with standard treatment and, it is believed, contributes to the achievement of the expected results with official treatment. Alternative medicine is used to replace the standard or official treatment\textsuperscript{20,21,39}.

The reasons for its use include iatrogenesis caused by allopathy, high cost of the official medicine, inability of conventional medicine to address the chronic degenerative diseases, and the vision that non-conventional medicine is more humane and personalized\textsuperscript{39-41}.

The advocates of non-conventional medicine believe that its popularity is due to the integral vision of the individual and to focus attention on the emotional state and the needs of the patient. The greatest criticism that the non-conventional treatments have received is related to the lack of scientific evidence. Though widely used, there is little information about their mechanisms of action, efficacy, and safety\textsuperscript{39,42,43}.

Phytotherapy and use of food supplements, especially high-dose vitamins, are among the methods used with most children. Also cited are homeopathy, spiritual treatments, prayer, relaxation techniques, and massage. Attention is drawn to the fact that non-conventional therapies are used even for pediatric common diseases\textsuperscript{39,44,45}.

The great interest and significant use of non-conventional medicine is a challenge to health professionals, who need to be alert to possible undesirable interactions and side effects of these treatments. However, it is of paramount importance that the medical team stays alert to the fact those patients and their parents, in general, do not inform that they are using non-conventional medicine in addition to the prescribed treatment. Both the medical team and parents should be informed about the benefits and adverse effects of such practices so that they can provide the best treatment for the child, preserving the continuity of conventional treatment\textsuperscript{39,46,47}.

**Conclusion**

Through this literature review it can be concluded that traditional methods of antineoplastic treatment include chemotherapy, radiotherapy, surgery, as well as the use of non-conventional medicine which can also be observed. Also the alterations of antineoplastic treatment (chemotherapy and radiotherapy) in the oral cavity, as well as to provide some subsidies for the professionals to control these alterations and thus improve patient quality of life.
Thus, it is suggested that the oncology treatment should be multidisciplinary. Those responsible for the children should understand that the sequelaes provided by the antineoplastic treatment can be avoided or soften and that the oral cavity involvement is not an obligatory thing. It is possible to improve these patients’ quality of life, but it is necessary to have health professionals, such as dentists and doctors, working together.

References


Recebido em: 18/04/2009
Aceito em: 27/06/2009

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Brazilian Journal of Health
v. 1, n. 1, p. 63-70, Jan/Abr 2010