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Current views of common pediatric cancers – an update

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Abstract. – Advancements in pediatric cancers diagnostics clarity and treatments have greatly increased survival rates in the pediatric oncology population. Increased survival rates have turned new attention to studying psychosocial stressors and improvisation of the quality of life of the suffering cancer patients. The cancer treatment experience could be divided into three phases: diagnosis, treatment, and post-treatment/survivorship. The present review article would focus specifically on the three most common pediatric cancer diagnostic categories viz. acute lymphoblastic leukemia (ALL), central nervous system (CNS) tumors, and neuroblastoma.

Key Words:
Pediatric cancer, Diagnosis, ALL, Neuroblastoma.

Introduction

The three most common categories accounting for 59% of all pediatric cancer diagnoses are acute lymphoblastic leukemia (ALL), central nervous system (CNS) tumors, and neuroblastoma[1]. Medical information specific to these diagnoses provided a context to understand psychosocial stressors related to pediatric cancer diagnosis, treatment, and post-treatment/survivorship. Pediatric cancer diagnosis in children involved observation of the symptoms associated with the pathological state like fatigue, dizziness, chronic pain, and/or abnormal bruising[2]. The above initial symptom presentation is typically followed by confirmation via medical tests that could be both invasive and painful in nature[3]. Based on results from medical evaluations and procedures, pediatric oncologists generally provided families a wealth of information about diagnosis, treatment options, and prognosis.

ALL Diagnosis

ALL is a cancer of lymphocytes or cells that form white blood cells. ALL begins when a young lymphocyte develops a series of mutations that transform the lymphocyte into a lymphoblast (i.e., leukemia cell). The lymphoblast then, multiplies uncontrollably and limits healthy cells in the bone marrow[4]. Lymphoblasts could spread into the bloodstream, lymph nodes, spleen, liver, and other organs. Clinically, children with ALL typically present signs and symptoms of marrow failure. Symptoms include fatigue, irritability, anorexia, and low-grade fever. Bone pain is also a common presentation and, in severe cases, could lead to abnormal gait or refusal to walk. Other concerning signs often-preceding diagnosis are pallor, bruising, and *petechiae*[5]. ALL could be detected and confirmed through a number of tests. An initial complete blood count (CBC) could be used to reveal abnormal blood counts (e.g., elevated white blood cells, low platelet count). A lumbar puncture could be used to detect spinal fluid lymphoblasts by looking at the spinal fluid through a microscope after the procedure is performed[2]. A physical examination and radiographic scans could reveal airway or pulmonary compromise associated with lymphoblasts and lymphomas. X-rays of the long bones might demonstrate "growth arrest" lines that frequently correspond with bone pain[5]. Physicians rely on a number of prognostic indicators to classify ALL patients' likelihood of long-term survival and appropriate treatment course. Age at diagnosis and initial white blood count (WBC) are among the most useful prognostic markers. Further, gender is also a prognostic marker, with females faring better than males and generally requiring a shorter duration of treatment. Lastly, response to initial treatment has become one of the most important prognostic indicators. Failure to achieve complete clinical remission at the end of induction chemotherapy has been associated with an extremely poor prognosis[6].

CNS Tumor Diagnosis

The central nervous system (CNS) tumors develop through a series of mutations in a CNS cell.

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These mutations cause CNS cells to multiply uncontrollably and form tumors. CNS tumors could be either malignant (fast-growing with a tendency to spread) or benign (slow-growing without a tendency to spread); however, all types of CNS tumors could be serious because they involved vital organs that control body functions such as movement, thinking, learning, breathing, and heart rate. Preceding and for some duration following diagnosis, children with CNS tumors typically present with symptoms related to raised intracranial pressure, such as headaches, vomiting, lethargy, and drowsiness. Other common symptoms included nosebleeds, back pain, and lower limb weakness[7]. In addition to undergoing blood draws and a lumbar puncture to examine the child's CBC and spinal fluid, children newly diagnosed with a CNS tumor must also undergo a staging and metastatic evaluation. This process generally included both non-enhanced and contrast-enhanced magnetic resonance imaging (MRI) of the brain and spine. MRIs inform the medical team of tumor invasiveness, location, and size of the tumor to allow proper diagnosis and treatment[7]. Prognosis for children with CNS tumors is most closely related to the age of the patient, nature of the disease at diagnosis and location of the tumor. Standard-risk CNS tumors include tumors that occur in children over the age of 3 years and without evidence of metastatic spread. However, the worst prognoses are generally for very young children or children with metastatic spread[7].

Neuroblastoma Diagnosis

Neuroblastoma is a type of solid tumor that involved developing cells in the sympathetic nervous system. Neuroblastoma begins when a young cell of the sympathetic nervous system, a neuroblast, begins to develop mutations and reproduce uncontrollably, forming cancerous tumors. Neuroblastoma could begin in various body locations, but it is most commonly found in the adrenal gland on top of the kidney. Neuroblastoma could spread to other areas including bone marrow, bones, and lymph nodes through metastasis. Neuroblastoma is a serious pathological state as it is associated with essential involuntary actions like heart rate, blushing, and dilation of the pupils[8]. Before diagnosis, children with neuroblastoma present quite varied signs and symptoms depending on primary tumor location and metastasis. Children with localized disease are often asymptomatic, while children with metastatic disease often experience fever, malaise, anemia, and bone pain like symptoms[9]. Other common initial symptoms are hypertension, tachycardia, headache, sweating, and flushing. Children with tumors located adjacent to or on the spine might show signs of spinal cord compression, such as weakness, paraplegia, and bowel/bladder dysfunction. Respiratory distress and organ compromise could also occur as a result of tumor location. An important component of the medical evaluation for neuroblastoma included a bone marrow aspiration to detect tumor cells. Examination of the tumor tissue is also an important factor for the staging of the disease. Further, a MRI could be helpful in evaluating the extent of the disease in patients with suspected spinal tumor and/or cord compression. Important prognostic factors for neuroblastoma are stage and age at the time of diagnosis. For all stages of neuroblastoma (1, 2, 3, 4, 4S), infants less than one year of age have a significantly better prognosis. Infants over age one year with stage 1, 2, or 4S are considered low-risk, while children over age one year and/or with stage 3 or 4 tumors are considered high-risk[10].

Psychosocial Adjustment to Diagnosis of Pediatric Cancers

The information about the diagnosis of cancer can invoke a wide range of emotional responses in the child as well as in the family[11]. This further results, with a marked increase in stress and with anxiety related symptoms are particularly pronounced in the first month following the diagnosis[12]. In fact, one study found that up to 43.7% of patients and parents reported significant symptoms related to post-traumatic stress disorder following pediatric cancer diagnosis[13]. Research has shown that parent post-traumatic stress, depression, and anxiety are significantly associated with caregiver's perceived role strain and parent-report of child emotional adjustment difficulties[14]. Further, parents who reported higher levels of parenting stress also reported higher levels of internalizing and externalizing problems in their children[15].

Treatment of Common Pediatric Cancers

Depending on the specific cancer diagnosis, cancer treatment usually included any one or combination of surgery, chemotherapy, radiation therapy, and bone marrow transplant. Surgical cancer intervention is generally used to remove tumors and for placement of a port that allows easier access to the child's bloodstream. Surgery is rarely sufficient as the sole treatment modality for cancer because of tumor metastases and risk of recurren-

ce. So, surgery is usually used in combination with chemotherapy and/or radiation therapy[16]. During chemotherapy, chemotherapeutic agents are administered orally, intravenously, intramuscularly, or into the spinal fluid to prevent rapid cell growth. Concurrent adverse side effects of chemotherapy are numerous and include nausea, vomiting, hair loss ("alopecia"), decreased appetite, chemotherapy induced cognitive dysfunction/impairment, mouth sores/mucositis, and low blood counts. Radiation therapy is typically used when chemotherapy and surgery were not able to eradicate a tumor. However, radiation therapy is associated with various adverse side effects, including fatigue, poor appetite, and irritation of the skin where radiation was directed[2]. In severe cases, radiation therapy administered to the CNS has irreversible side effects, such as decreased white brain matter resulting in significant learning impairments and neurocognitive deficits. Fortunately, improvements in CNS radiation, such as focal radiation (e.g., proton therapy), have allowed the use of smaller radiation doses and decreased severity of neurocognitive late effects[17]. In the last treatment option, a new bone marrow was administered intravenously to produce new blood-forming tissue (bone marrow transplant). However, patients are at acutely high risk for infection and graft-*vs*.-host disease, (in which the recipient's body rejects new tissue) during the transplant as well as after several months of bone marrow transplant.

ALL Treatment Overview

The course for ALL treatment is tailored to the predicted likelihood of relapse (based on prognostic indicators and, sometimes, genetic typing) and included multiple phases that typically span two to three years. The first treatment phase for ALL is induction therapy (i.e., chemotherapy agents). The goal of induction is to rapidly eliminate as many malignant cells as possible. A combination of up to four chemotherapy agents might be used based on the leukemia cells' projected course[5]. Following the induction phase, a consolidation chemotherapy phase might be indicated. Consolidation is designed to expose leukemia cells to non-cross-resistant drug combinations and for CNS prophylaxis. Upon remission, intensification of chemotherapy agents resulted in a significant improvement in event free survival[18].

CNS Tumors Overview

The standard treatment approach for CNS tumors included complete or near-complete surgical excision of the tumor, which is followed by a post-operative craniospinal radiation therapy (CSRT) and chemotherapy. Radiation therapy is a critical component of CNS tumor treatment and quality of radiation therapy is essential for the successful management of the disease. Along with surgery and radiation therapy, chemotherapy might be included in the treatment plan to further manage the disease and risk of recurrence[7]. CNS tumor treatment duration generally depends on tumor volume, location and could extend from a day for surgical tumor excision to several years[19].

Neuroblastoma Treatment Overview

It has been observed in the recent past that surgery alone has resulted in 95% survival rate of neuroblastoma patients with stage 1 or 2. For high-risk neuroblastoma patients (stage 3 and 4), best treatment results have been related to intensification of induction therapy, mega therapy consolidation, bone marrow transplant, and supportive care. Surgical intervention of the tumor might also be an option for high-risk neuroblastoma; however, high surgical risks and potential surgical morbidity must be considered. Due to uncertainty about effectiveness with neuroblastoma, radiation is typically used only in high-risk stage 4S of neuroblastoma tumor treatment[20]. Neuroblastoma treatment varies widely in duration, from a tumor removal day surgery for low-risk patients to several years for high-risk patients.

Psychosocial Adjustment to Cancer Treatments of Common Pediatric Cancers

As activities related to cancer treatment begin to take the forefront in patients' daily life, disruption in patients' participation in academic pursuits, extracurricular activities, and physical activities occur because of weakness, pain, risk of infection, and frequent medical appointments and hospitalizations[21]. Related to social functioning, the high intensity and side effects associated with chemotherapeutic agents, radiation, and bone marrow transplant could lead to marked changes in the patients'social inclusion[22]. Limited age normative activities (e.g., physical activity, sports) due to greater risk of infection, increased fatigue, general malaise, or overall perceptions of being different from peers could also negatively impact patients' social development during cancer treatment[21]. Additionally, childhood cancer diagnosis increased the likelihood of parental overprotection and parents' perceptions of child vulnerability[23]. The literature further suggested

that the presence of overprotective parenting and parents' perception of child vulnerability is positively related to children's poor emotional adjustment and social behaviors during, as well as after, cancer treatment[24].

Post-treatment/Survivorship Overview

Successful diagnosis of pediatric cancer diagnosis allows survival of at least five years more than 80% pediatric patients. Such promising survival rates reflected the importance of understanding post-treatment medical, cognitive, and late psychosocial effects that could place children at risk for peer victimization. Adherence to physician-prescribed medication regimens (i.e., following medications/self-care after acute hospital care) and routine follow-up medical appointments are defining features of the post-treatment process, especially in early survivorship phase. The late effects of various cancer treatments could impact childhood cancer survivors' development. Medical late-effects related to a variety of cancer treatment modalities included cardiomyopathy, hypothyroidism, obesity, short stature, infertility, and risk of a second cancer diagnosis[25,26]. The late effects of ALL have been observed to be typically present in cardiac, orthopedic and neurologic complications[27]. Childhood cancer survivor studies have also reported significant deficits in survivors, cognitive functioning, short-term memory, processing speed, visuomotor coordination, sequencing ability, and academic achievement. In CNS tumors, craniospinal radiation therapy is responsible most of the times for the late effects. Due to rapid brain development, children receiving radiation therapy before the age of 3 years often-evidenced late effects like brain tissue damage, significant growth impairment, endocrine dysfunction, and hearing loss[28]. Other cognitive difficulties apparent in survivors are related to attention deficits, slower processing speeds, and executive functioning problems[29]. Late effects from neuroblastoma are usually related to long-term chemotherapy-related complications that included neurologic and developmental problems[30]. Late effects are typically most pronounced for high-risk disease patients and for low-risk disease patients who experience spinal cord compression. For high-risk neuroblastoma survivors, late effects included significant growth problems, secondary malignancies, and hearing loss. On the other hand, for the low-risk neuroblastoma survivors who experienced spinal cord compression, late effects included scoliosis and gait problems.

Conclusions

The three most common pediatric cancers are ALL, CNS and neuroblastomas. Further, a lot of developments have been made in both the diagnosis as well as treatment of these pathological states, but post-treatment period of survivors is often associated with late effects. Future studies are recommended for the eradication of these late effects.

Conflict of interest

The authors declare no conflicts of interest.

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