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Review Article

Infant Cancer Chemotherapy

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ABSTRACT

Cancer is the abnormal, excessive, uncoordinated, autonomous and purposeless proliferation of cells even after the cessation of stimulus for growth which caused it. Cancer occurring in infants often has both clinical and biological properties that are different from those of the same histologic type of cancer diagnosed in older patients. Infant cancers tend to be more aggressive and progresses more rapidly than adult cancers. But with some exceptions, infant cancers respond better to certain treatment than adult cancers do. Worldwide, it is estimated that infant cancer has an incidence of more than 175,000 per year, and a mortality rate of approximately 96,000 per year. Infant cancers are not always treated like that of adult cancers. Pediatric oncology is a medical specialty focused on the care of children with cancer. In developed countries, infant cancer has a mortality of approximately 20% of cases. In low resource settings, on the other hand, mortality is approximately 80% or even 90% in the world's poorest countries. In many developed countries the incidence is increasing at a faster rate each year.

Key Words: cancer, chemotherapy, oncology.

INTRODUCTION

Every cell in the body has a system that controls its growth, interaction with other cells, and even its life span. The proliferation and maturation of cells in human body is controlled as a result of which some cells proliferate throughout life (labile cells), some have limited proliferation (stable cells), while others do not replicate (permanent cells). On the other hand, cancer cells lose control and regulation of replication. Infant cancer is rare and comprises a heterogeneous group of neoplasm with substantial histological diversity. [1] Almost all types of childhood cancer can occur in fetal stage however, the presentation and behaviour of neonatal tumors differs from that in older children, leading to differences in diagnosis and management. [2] In children, cancers grow and spread more rapidly, hence pediatric cancers are often diagnosed at a later and more advanced stage than adult cancer. In India, cancer is the 9th common cause for the deaths among children between 5 and 14 years of age. [3] The causes of infant cancer are unclear, but genetic factors probably have a key role. Other congenital abnormalities are frequently present. The types of cancers that occur most often in children are different from those seen in adults. The most common cancers of children are acute lymphoblastic leukemia, acute myeloid leukemia, myeloid leukemia, Hodgkin lymphoma. [4]

Table 1: Common types of cancer seen in children

1	Hematologic	Acute lymphoblastic leukemia
		Acute myeloid leukemia
		Myeloid leukemia
		Non Hodgkin lymphoma and Hodgkin lymphoma
2	Central nervous system	Medulloblastoma
		Ependymoma
		Brainstem gliomas
		Low- and high-grade gliomas
		Germ cell tumors
3	Solid tumors	Neuroblastoma
		Ewing sarcoma
		Osteosarcoma
		Wilms tumor
		Rhabdomyosarcoma
		Other soft tissue sarcomas
4	Other tumors	Retinoblastoma
		Hepatoblastoma

CAUSES

The actual causes of most infant cancers are not known. About 5 percent of all cancers in infants are caused by an inherited mutation. But most infant cancers are not caused by inherited DNA changes. They can also occur as a result of acquired mutation, that happens early in a child's life, sometimes even before birth. Most cancers in children, like those in adults, are thought to develop as a result of mutations in genes that lead to uncontrolled cell growth and eventually cancer. [5] In adults, these gene mutations reflect the cumulative effects of aging and long-term exposure to cancer-causing substances. However, identifying potential environmental causes of infant cancer has been difficult, partly because cancer in children is rare and partly because it is difficult to determine what children might have been exposed to early in their development. [6]

2.1 Problems with development in the womb

Infant cancers such as Wilm's tumours (kidney cancer in children) and retinoblastomas (eye cancer in children) begin when the baby is still inside their mother's womb. When a baby starts growing in the womb, many parts of the body, such as the kidneys and eyes, develop very early on. Sometimes something goes wrong and some of the cells that should have turned into mature cells to form a part of the body don't. Instead they remain as very immature cells. Usually, these immature cells don't cause any problems and mature by themselves by the time the child is 3 or 4 years old. But if they don't, they may begin to grow out of control and develop into a cancerous tumour. [7,8]

2.2 Exposure to infections

Epstein Barr virus (EBV) is a common infection in infants. It usually causes no symptoms. But, it can cause glandular fever (infectious mononucleosis) in teenagers and young adults. While glandular fever can be very unpleasant, it usually passes within weeks and it doesn't mean that one can go on to develop cancer. [9] Once infected, a person remains a carrier of EBV for life, but the virus normally doesn't cause any symptoms at all. In rare cases, infection with EBV can contribute to the development of cancers such as Hodgkin lymphoma and Burkitt's lymphoma. Most people get infected with EBV as a child and stay infected for life without ever experiencing any symptoms. Because of how common it is, there is nothing that can be can done to prevent it, or your child, coming into contact with EBV at the moment.

2.3 Exposure to radiation

Radiotherapy is used as a treatment for cancer where ionizing radiations are used. Infants who have radiotherapy for cancer have a slightly greater risk of developing another type of cancer later on. But the risk is small compared to the risk to their health if the original cancer had not been treated with radiotherapy. [10] Radon gas is a natural radioactive gas and it is a type of ionizing radiation. Radon gas is

found in the air at a low level outdoors, but it can sometimes build up to high concentrations indoors. Because it is a natural gas, it is difficult for us to control our exposure to it. Overall, studies so far have only suggested that there might be a weak link between indoor levels of radon gas and risk of childhood leukemia. [11]

2.4 Previous cancer treatments

Past treatment with chemotherapy can increase the risk of cancers such as acute leukaemia many years later in children and adults.

TREATMENT

The treatment of cancer in infants include surgery (to remove cancerous cells or tumors), chemotherapy (the use of medical drugs to kill cancer cells), radiation (the use of radiant energy to kill cancer cells), and bone marrow transplant. [12]

3.1 Surgery

For infants with leukemia or lymphoma, surgery is not usually the main treatment as leukemia and lymphoma involve the circulatory system and the lymphatic system, two systems that are located throughout the body. This makes it hard to treat these cancers by operating on just one area. However, in infants with solid tumors that haven't spread to other parts of the body, the preferred treatment is surgery combination in with chemotherapy and/or radiation. [13]

3.2 Radiation

Radiation is one of the most common treatments for cancer. A child who receives radiation therapy is treated with a stream of high-energy particles or waves that destroy or damage cancer cells. Many types of infant cancer are treated with radiation along with chemotherapy or surgery. Radiation therapy is often used in the treatment of rhabdomyosarcomas, non-rhabdomyosarcoma soft tissue sarcomas, Ewing tumors, osteosarcoma, medulloblastomas, ependymomas, germ cell tumors in the brain, retinoblastoma, advanced Wilm's tumor, neuroblastoma, and Hodgkin's disease. [14] Though radiation therapy is a powerful tool to cure infant cancer, it has many side effects. The nature and severity of side effects depend on the tumor's location and type, its extent and radiation dose. Side effects can occur at any time after treatment, even 50 years later. Growing tissue in children is particularly susceptible to radiation therapy. Brain tissue in the very young can be damaged by very low doses of radiation and growing muscle and bone may also show signs of reduced potential growth following low doses of radiation. For this reason, most of the normal tissue in children is avoided as far as possible. [15] In addition, radiation has the potential risk of causing another tumor many years after treatment. These can be benign or malignant. The smaller the volume of tissue treated, lesser is the risk. [16]

3.3 Bone Marrow Transplants

Infants with certain types of cancer may receive bone marrow transplants. If a child has a type of cancer that affects the function of blood cells, a bone marrow transplant (along with chemo to kill the defective cells) may allow new, healthy cells to grow. [17] Bone marrow transplants are also sometimes used to treat cancer that does not involve blood cells because they allow doctors to use higher doses of chemotherapy than a child would normally be able to take.

3.4 Chemotherapy

Chemotherapy (chemo) is medicine that can eliminate cancer cells in the body. Infants with cancer can take the chemotherapy medications intravenously (through a vein) or orally (by mouth). Some forms of chemotherapy can be given intrathecally, or into the spinal fluid. [18] The drugs enter the bloodstream and work to kill cancer cells throughout the body. How long chemo lasts and the type and number of different drugs used depends on the type of cancer and how well a child's body responds to the treatment. Every child's treatment is different, so a child may receive daily, weekly, or monthly chemotherapy treatments. The doctor also may recommend cycles of treatment, which allow the body to

rest and recover between periods of chemo. All of the medicines used in chemotherapy carry the risk of both short-term and long-term problems. In the short term after getting chemotherapy, a child might have: nausea, vomiting, hair loss, fatigue, anemia, abnormal bleeding, and kidney damage. Because chemotherapy destroys bone marrow, it can increase the risk of infections. Some drugs irritate the bladder and may cause bleeding into the urine, hearing loss, and liver damage. [19] Others may cause cardiac and skin problems. Longer-term effects can include infertility, growth problems, organ damage, or increased risk of other cancers. Doctors always take side effects into account before giving chemotherapy and may use medicines to protect patients against as many of the side effects as possible. [20] The determination of appropriate dosing regimens for the treatment of infants and very young children with cancer represents a major challenge in paediatric oncology. Whereas dose reductions are commonplace for many chemotherapeutics in this patient group, the appropriateness of dose reductions for drugs is unclear when the limited numbers of published studies reporting on pharmacokinetics in infant patient populations are considered. [21]

3.4.1 Acute lymphoblastic leukemia

Infants should received two courses of induction therapy with idarubicin, Ara-C, and etoposide followed by two consolidation courses (high-dose Ara-C combined with etoposide and mitoxantrone during the first and second course respectively). [22] The post-remissional treatment is based on autologus or allogeneic hematopoietic stem cell (HSC). Although the long-term toxicity associated with hematopoietic stem cell transplantation cannot be neglected, in view of the high risk characteristics of almost all infants, transplantation holds the potential to still qualify as the treatment associated with the lowest risk of leukemia recurrence, in particular in subgroups of infants with worst prognosis (i.e., those with more than 5% blasts at the end of induction therapy or those carrying unfavorable cytogenetic/ molecular lesions). [23]

3.4.2 Acute myeloid leukemia

Earlier studies have recommended two remission induction regimens, which include N(4)-behenoyl-1-beta-D-arabinofuranosyl cytosine with idarubicin and in resent studies used cytarabine with idarubicin or mitoxantrone which resulted in similar overall response rates of approximately 85%. [24] Modified regimens, such as via varying doses or types of anthracyclines, the addition of other agents, and the intensification of cytarabine, have resulted in remission rates similar to those obtained with the standard combination of daunorubicin and cytarabine. [25] Recent advances in supportive care, along with the various trials of chemotherapy regimens, have also contributed to improved therapeutic outcomes. Supportive care to reduce the risk of early complications related to the primary disease or to toxicity of chemotherapy and to manage infections, such as bacterial or fungal pathogens, has also steadily improved over the decades. [26] Postremission chemotherapy includes some of the drugs used in induction while also introducing non–cross-resistant drugs and, commonly, high-dose cytarabine. Studies in adults with AML have demonstrated that consolidation with a high-dose cytarabine regimen improves outcome compared with consolidation with a standard-dose cytarabine regimen. AML subtypes Randomized studies evaluating the contribution of high-dose cytarabine to postremission therapy have not been conducted in infants, but studies employing historical controls suggest that consolidation with a high-dose cytarabine regimen improves outcome compared with less intensive consolidation therapies. [27] All contemporary pediatric trials include intrathecal chemotherapy (cytarabine, methotrexate, or both with hydrocortisone) to prevent CNS relapse, which occurs in less than 5% of patients. [28] Although most investigators recommend intrathecal

cytarabine alone, the optimal components of intrathecal therapy for infants with AML remain unclear. Studies recommend 4 monthly doses of intrathecal cytarabine, methotrexate, or both with hydrocortisone for patients without CNS leukemia at the time of diagnosis and 8 doses (4 weekly doses followed by 4 monthly doses) for patients with CNS disease. Children with AML are also at risk of invasive fungal infections, most commonly caused by Candida and Aspergillus species. [29] Again, randomized, controlled trials of antifungal prophylaxis in children with cancer are lacking, but the results of multiple studies conducted in adults with cancer support the use of these agents that all children with AML should receive antifungal prophylaxis; voriconazole, posaconazole, micafungin, and caspofungin are all reasonable choices. Because of drug interactions and variable pharmacokinetics, voriconazole and posaconazole should not be held during courses of chemotherapy, and levels of voriconazole and posaconazole should be maintained through levels greater than 1 μg/mL and should be checked periodically. [30]

4.3.3 Hodgkin lymphoma

Each cycle of ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) should last for 28 days, with chemotherapy administered on Days 0 and 14. Adriamycin 25 mg/m^2 IV, Bleomycin 10 units/m^2 IV, Vinblastine 6 mg/m2 IV, Dacarbazine 400 mg/m^2 IV. The absolute neutrophil count (ANC) must be greater than 500 x 106 /L and the platelet count must be greater than 75 x 109 /L. Granulocyte colony stimulating factor (G-CSF) can be used at the treating physician's discretion in order to maintain the every two week timing for chemotherapy administration. [31] The most commonly encountered hematological toxicity on this protocol is leucopenia and neutropenia. For most patients this is self resolving and does not impact on the administration of subsequent doses of therapy. However occasionaly this may be more prolonged and could result in delay in administration of the subsequent cycle of therapy. In such patients granulocyte colony stimulating factor (GCSF) may be used at a dose of 5 mcg/kg/dose at a schedule that is decided upon by the treating physician. [32] Discontinue doxorubicin for clinical or echocardiographic evidence of cardiomyopathy (shortening fraction (SF) < 27% or left ventricular ejection fraction (LVEF) < 50%). Doxorubicin should not be routinely administered to such patients who have developed cardiac toxicity. Pulmonary fibrosis is a serious risk with the use of Bleomycin. However, although it may occur, pulmonary toxicity below a cumulative dose of 150 units/m^2 is rare. The cumulative dose on this protocol is 80 units/m^2. Patients experiencing dry cough, dyspnea, rales and pulmonary infiltrates should be evaluated for potential pulmonary toxicity at any cumulative Bleomycin dose, as a distinct hypersensitivity pneumonitis is recognized at any dose. Patients with the above signs and symptoms should be evaluated by the pulmonology service and should undergo pulmonary function studies. [33] Patients with documented pneumonitis should be treated with corticosteroids and should not receive any further doses of Bleomycin. Doxorubicin and Dacarbazine are both highly emetogenic agents. In addition there is an incidence of delayed emesis with these agents. All patients should receive either ondansetron or granisetron and dexamethasone intravenously prior to the chemotherapy. Patients should also receive oral antiemetic agents (ondansetron) for 24- to 48-hours following the chemotherapy. Longer duration of antiemetic therapy may be required in a few patients. [34]

4.3.4 Wilm's tumor

Surgery is the cornerstone for the treatment of Wilm's tumor. The Children's Oncology Group (COG) from North America, a group that conducted the NWTS trials, recommends surgery before chemotherapy, whereas SIOP in Europe suggests preoperative chemotherapy. [35] As the SIOP group, the National Wilms Tumor

Study Group (NWTSG) has concerns about performing a biopsy first because of the risk of tumor upstaging. [36] The SIOP recommends preoperative chemotherapy to decrease the risk of intraoperative rupture, downstage the tumor, and to reduce the need for irradiation. The advantage of preoperative chemotherapy is the identification of chemoresistant high-risk blastemal predominant subtype that benefits from treatment intensification. Chemotherapy for Wilm's tumor include Single-agent vincristine at 50 % reduced dose level (0.16 mg; 0.75 mg/m^2) if the birth weight of the infant is 3.3kg and the number of treatment required is 10. [37]

4.3.5 Neuroblastoma

According to the COG and Pediatrics Oncology Group guidelines for neuroblastoma treatment, and the characteristics of during neuroblastoma diagnosis (the size and location of the primary tumor, metastasis and the tolerance degree to surgery), the neuroblastoma treatments include capacity reduction chemotherapy prior to surgery, chemotherapy after surgery, and high-dose chemotherapy combined with ABPSCT. [38] Carboplatin: 10 mg on days 1,2 and 3; Etoposide: 8 mg on day 2, 12.5 mg on days 3/4; Vincristine: 0.28 mg on day 4. According to COG guidelines, patients should receive either a carboplatin, etoposide and melphalan (CEM) regimen or busulfan/melphalan. Patients with bone metastasis or bone marrow metastasis should receive ^{131}I-metaiodobenzyl-guanidine (^{131}I-MIBG) prior to pretreatment.

CONCLUSION

The diagnosis and treatment of childhood cancers takes time, and there are both short-term and long-term side effects. But with advancements in medicines, more and more infants with cancer are finishing successful treatment, leaving hospitals, and growing up just like everybody else. Today, more than 80% of all children with cancer live 5 years or more. The overall improvement may in part be attributed to improved supportive care in the intensive-care setting for acute infections and toxicity related to intensive chemotherapy and also for metabolic complications, life-threatening hemorrhage, and other effects of the disease on organ function.

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