

Cancer Treatment Response Differences in Pediatric and Adult Cancers

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Abstract. There are significant differences between childhood and adult cancers in a number of ways, including causes, treatments, and response to treatment. Childhood cancers are often associated with factors such as germline predisposition, genetic mutations, viral infections, and exposure to toxic substances. In contrast, adult cancers may be more influenced by factors such as family history, long-term exposure to radiation, and poor lifestyle habits. Although both childhood and adult cancers may be treated with chemotherapy, radiotherapy, and immunotherapy, treatment for children requires special attention to dose optimization and minimization of long-term side effects. In addition, the treatment of pediatric cancers presents some special challenges. The relatively low incidence of childhood cancers, the large tumor heterogeneity, and the fact that the needs and responses of each child may be different have led to relatively slow progress in pediatric oncology research. At the same time, due to the immature functioning of body systems in children during development, treatment requires more careful consideration of various possible side effects and implications. Therefore, this article first analyzes the differences in the causes of cancer between children and adults, then, explores the differences in cancer treatment between the two, and finally, emphasizes the need for collaborative efforts to address these challenges, improve access to care, and increase survival rates for pediatric patients with cancer.

Keywords: Cancer; Childhood; Pediatric cancer; leukemia; Immunotherapy.

1. Introduction

Cancer, one of the biggest challenges in medical history, is a disease concerning all populations. Often, cancer is more subjected to adult patients, as it is mostly considered to be related to the age of the patient. As a person gets older, cells go through more cycles of proliferation and the chances of a random mutation occur. Then, cancerous cells can emerge as mutations accumulate to form malignancy. However, cancer is not only found in aging populations. Pediatric cancer, although rarer in comparison, Pediatric and adult patients often vary in medical diagnosis procedure, and treatment to a certain degree. This difference is rooted in the physiological differences between age groups, significantly different stages of development would contribute to this as well. The major difference lies in the types of cancer.

In adult patients, the most prevalent cancers are located in the lungs, colon, breast, prostate, and pancreas. This prevalence is often due to turnover rates and functionality of the specific tissues due to age. For pediatric cancer, it is often quite rare and frequently aggressive. Pediatric cancer is hard to diagnose as symptoms often parallel other common diseases. The common types include blood cancers (leukemia), brain tumors, lymphoma, and central nervous system (CNS) tumors (such as neuroblastoma). The trigger for the prevalence of blood cancers is often unknown. The difference in sites of cancer found also indicated that they are usually of different causes. The cause of pediatric cancer is usually not due to carcinogen exposure in the forms of smoking or alcohol consumption, which are prevalent in adults.

2. Physiology and Molecular Pathway Differences

Cancer often takes form in somatic mutations, meaning that the patient acquires the mutation in the body later on in life. Cancer is not passed on from generation to generation and is often not inherited. However, it is likely to inherit allelic mutations that make a person more prone to cancer.

For instance, the infamous BRCA 1 mutation can lead to a high risk of breast cancer. In pediatric cancer, around 8-10% of all patients are found to have inherited these predisposing factors, making this the most prominent cause currently known [1]. For instance, retinoblastoma, a rare infant retina disease, is formed when the retinoblastoma gene (RB1) alleles are mutated. As a tumor suppressor gene, the mutation would cause tumor progression in the eye. Around 45% of retinoblastoma pediatric patients inherited one mutated RB1 allele from one of their parents. [2] This makes them more susceptible to mutation accumulations, causing cancerous tumors. Similar to adult cancers, pediatric cancer can also be a result of mutations of genes. This happens early in development. For instance, trisomy 21 is caused by a mistake that takes place during germline cell meiosis. The zygote has an extra copy of chromosome 21. This markedly elevates the likelihood of developing leukemia in patients with Down syndrome, although a decreased risk of developing solid tumors [3]. Although unlikely and hard to identify, environmental causes can lead to pediatric cancer as well. However, this is more concentrated on sources accessible to the child, for instance, UV-induced melanoma or X-rays during pregnancy pre-natal. The cause of adult cancer is similar. However, according to the WHO, they are more significantly reliant on external carcinogen contacts and age. Common carcinogens include asbestos, tobacco smoke, alcohol, UV light, and ionizing radiation [4]. The risk of cancer is still elevated by potential genetic predispositions, following a multi-hit mutation model that requires accumulating mutations for tumors to form and become malignant. For both adult and pediatric cancers, the mutation can often take place in many forms, resulting in different phenotypes. Some examples include those mentioned in Figure 1 where chromosomes can experience changes in numbers, amplifications and deletions, and translocations [5]. These all bring changes to the genetic information that the chromosomes carry. Although, many of the body's mutations are silent, where no phenotype is altered. Additionally, the body has damage control mechanisms in response to DNA damage. Thus, the rate of mutation is low, and it takes many mutations accumulated together to lead to a cancerous cell [6].

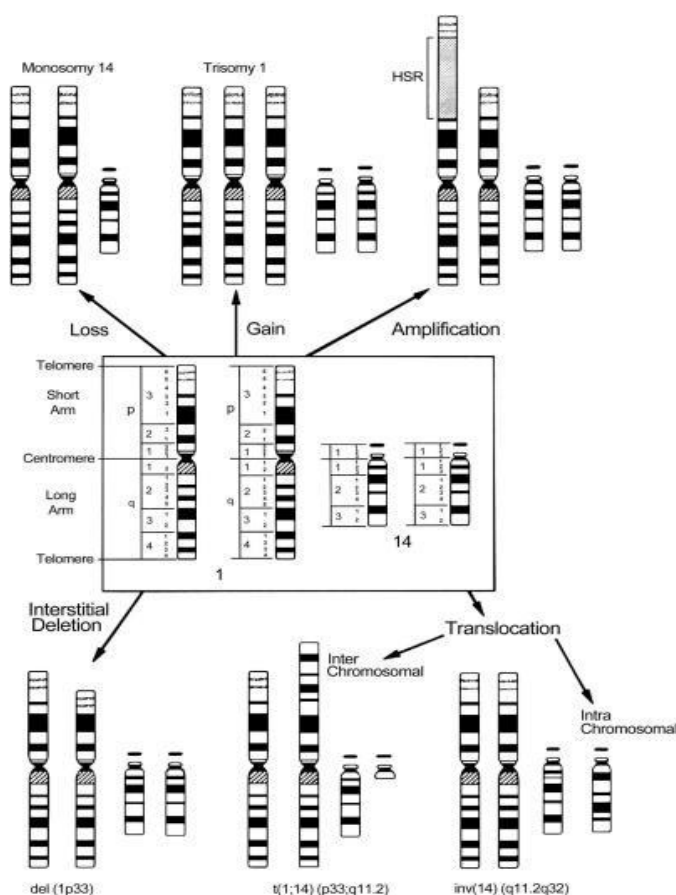


Fig 1. Chromosomal aberrations of chromosomes 1 and 14. Kirsch IR: Molecular basis of childhood cancer [5].

Aside from differences in cause, adult and pediatric cancer also varies in terms of physiological pathways. The accumulation of mutation just leads to abnormal cell proliferation and tumor formation. To become a cancer cell, it would require the tumor cells to do more than excessive proliferation. This includes inhibiting apoptosis, protruding into surrounding tissues and the bloodstream (angiogenesis), replicative immortality, and suppression of immune efficiency. In pediatric cancers, a lot of the causes are in utero, where development plays a big role. For instance, germline TP53 variants develop *de novo*, leading to various pediatric cancers including Acute Lymphocytic Leukemia, adrenocortical carcinoma, Sonic Hedgehog medulloblastomas, and more [7]. There are more germline gene mutations as such that can make certain types of cancer more prevalent in pediatric cancer as compared to adult cancers (Figure 2) [7].

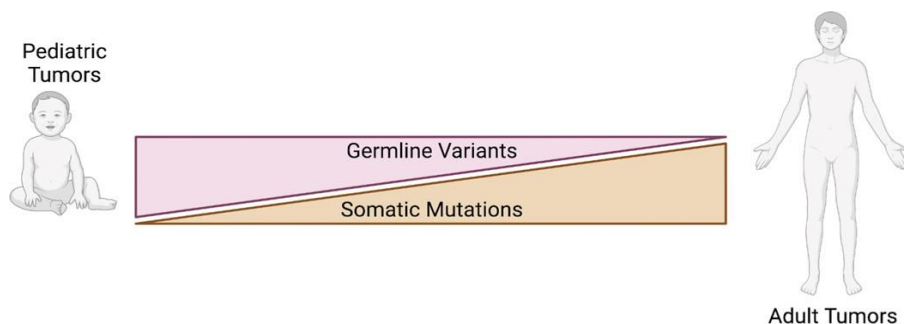


Fig 2. Comparison of Ratio of Germline versus Somatic Mutations in Pediatric and Adult Cancers [7].

3. Treatments and Pharmacokinetics

There are many treatments for cancer. The most standard current treatments include surgical removal of the malignant masses, Chemotherapy, Radiotherapy, and Immunotherapy. There are side effects and concerns to each of these treatment options, although the considerations vary between adult and pediatric cancer patients. Due to physiological differences, adult cancer treatment focus is often different from pediatric cancer treatment. Pediatric cancer is very careful with minimizing damaging, long-term side effects chemotherapy is administered at a larger dosage for pediatric cancer patients as compared to adults. In the United States, pediatric cancer therapies have achieved great advances over the last 70 years, and the overall survival (OS) rate for pediatric cancer patients has reached 80%. However, cancer is still the top cause of death by disease in children [7].

Conventional chemotherapy plays an important role in pediatric cancer treatment, especially in lower to middle-income countries [8]. However, post-therapy survivorship can be challenging for children with various side effects. As a quite invasive therapy, chemotherapy targets the cells that are proliferating quickly and kills those cells with cytotoxicity. This includes not only the cancer cells, but also hair cells, stomach lining cells, and oral mucosa cells. Thus, common side effects include hair loss, stomach and oral ulcers, and prone to infections. While these side effects are also prevalent in adult chemotherapy recipients, In terms of radiotherapy, is used much less in therapy due to the uncertainty of the effects and potential long-term causes. Radiation therapy is a gain and loses balance as exposure to radiation can lead to new mutations arising in the body. There is a risk of increased tumors in previously undiscovered organs. This is named secondary cancer. This is because radiotherapy and chemotherapy can be carcinogens themselves. A comprehensive nationwide investigation into cancer cases prior to the age of 22 revealed that an accumulated dose of 50 milligrays (mGy) could potentially triple the risk of leukemia, and a dosage of 60 mGy could elevate the risk of central nervous system (CNS) tumors to the same fold[9].

Immunotherapy is a really promising field for pediatric cancer therapy, especially in the case that leukemia is the most prevalent cancer type. Currently, the most effective FDA-approved treatment is monoclonal antibody immunotherapy, Ipilimumab [7]. It targets colorectal cancer and melanoma. Additionally, pembrolizumab, administered to target PD-1 is also very efficient at treating Hodgkin

Lymphoma, Non-Hodgkin Lymphoma, Merkel Cell Carcinoma, and Solid Tumors [7]. Chimeric Antigen Receptor T-cell therapy, more well-known as CAR T-cell Therapy, is another effective type of adoptive T-cell immunotherapy. In a simplified manner, CAR T-cell therapy is the engineering for stronger T-cells ex-vivo and then transfusion back to the patient to promote better tumor cell cytotoxic functions. First, T-cells are collected from patient samples through a process of leukapheresis, where only specific abnormal white blood cells are collected. Then, genetic engineering allows for chimeric antigen receptors (CARs) to be expressed on the surface of the patient's T-cells ex-vivo. These receptors are expressed on cytotoxic T-cells where its antigen-binding ectodomain recognizes tumor cell antigens. This effectively prompts signal transduction and exocytosis of cytotoxic granules. Thus, this can lead to the apoptosis of the antigen-expressing cancerous cells. Currently, CAR T-cell therapy is effective in blood cancers, including leukemia and lymphomas. However, the rate of remission and relapsing multiple times is high in both children and adults upon treatment [10].

Pharmacokinetics in pediatric cancer is dependent on physiological differences from adults. The dosage of treatments is important to determine therapeutic efficacy, but also the toxicity and side effects. There are four main processes of pharmacokinetics: metabolism, drug absorption, distribution, and excretion. Metabolism of drugs is highly dependent on the pathways involved and other drugs that might be already in effect in the body. For instance, Azole antifungals are often used in pediatric cancer treatment, since patients under chemotherapies can be quite susceptible to infections. They are strong inhibitors for transport proteins like P-glycoprotein. When Azole is administered with certain chemotherapy drugs such as Vinca alkaloids and calcineurin inhibitors, there can be increased toxicity. Pharmacokinetics of drug absorption is dependent on a low bound of minimal effective concentration (MEC) and a high bound of minimum toxic concentration (MTC) or maximum tolerated dose (MTD). This is calculated by body weight or body surface area. However, due to the lack of data from pediatric patients, this is very difficult to determine. There is not a big population for pediatric cancer patients in comparison to adult cancer patients, enough to create a guideline for drug administration for future patients. The current method is to extrapolate from adult dosage per kilogram body weight to find the pediatric situation. However, extrapolation is not always the most trustworthy as individual metabolism and developmental changes can play a huge role in drug uptake. Last but not least, the excretion of the drug is the removal of the drug and side products from the body in the form of urination, sweat, breath, or feces. It can be quantified by the clearance rate of compound per unit of time. An important concept in clearance is the half-life of the drug. An example of the importance of dosage is that for Voriconazole, another antifungal drug, the concentration of which half of the maximum enzyme activity is achieved is higher in children. The linearity of the drug excretion is thus compromised in adults [11].

4. Conclusion

Cancer does vary by age group, in all aspects from etiology and molecular pathways to treatment and pharmacokinetics. Despite significant advances in cancer research and growing understanding of cancer in recent years, pediatric cancer research still requires more attention and commitment from future researchers. An important issue facing pediatric cancer research is the relatively low incidence of the disease. The small number of pediatric cancer patients compared to adult cancers somewhat hinders research progress and creates challenges in developing personalized and targeted therapies for individual patients. This limitation of disease modeling may affect research progress.

In addition, the heterogeneity of childhood cancers is a challenge in determining optimal treatment strategies. As mentioned earlier, the etiology of cancer is complex and diverse and may involve both genetic susceptibility and environmental exposures. Further differentiation may occur through individual pathways and immune responses to tumors, making diagnosis and targeted therapy more difficult. At the same time, pediatric cancer treatment is strongly associated with long-term side effects. Some invasive treatments may have challenging long-term effects on children, including toxicity to organs or secondary cancer development. Therefore, when treating childhood cancers,

there is a need to weigh the efficacy against the potential risks to ensure that the child is cured of the disease while minimizing adverse effects and sequelae.

To address these challenges, the collaboration and efforts of a multidisciplinary team are required. Researchers, clinicians, policymakers, and advocates should work together to improve access to care and increase survival for pediatric cancer patients. Through increased collaboration and communication, physicians can better understand the characteristics and needs of childhood cancers, promote the development and application of personalized treatment plans, and bring safer and more effective treatment options to children.

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