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Advances in Genetic Therapies Concerning Pediatric Leukemia

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Cancer affects the cells in the body, where they divide uncontrollably and can spread to other areas. Cancer starts from a single cell and can grow to over a trillion cells. These cells are damaged in their genetics, which allows them to grow in great numbers. Although there can be benign tumors, cancer is malignant, meaning these cells spread throughout the body. Blood cancers such as leukemia are cancers of the blood which does not form tumors. Pediatric leukemia is one of the most common malignant cancers in children. Most children affected by this cancer are two to five years old, while children affected by acute myeloid leukemia (AML) are around ten. These cancers are more common in children, but this kind of cancer can develop in people of any age. Some of the most common treatments for this disease are chemotherapy or radiation. However, therapies have drastically improved for these cases, especially those with ALL. Unfortunately, the progress for AML has been slower for all age groups. In this paper, we will delve deeper into the causes and predispositions for leukemia and the recent progress in the treatments for this disease.

Introduction

Leukemia is cancer that affects the blood. Leukemia is most common in children under fifteen, although it can occur at any age. Four kinds of leukemia exist acute lymphoblastic (ALL), acute myeloid (AML), chronic lymphoblastic (CLL), and chronic myeloid leukemia (CML). Acute and chronic leukemia differ by acute, meaning fast-growing, while chronic grows slowly. ALL affects nearly 80% of all pediatric cases (Madhusoodhan et al., 2016). In these cases, the Caucasian and Hispanic populations are most likely to develop this cancer. In addition, males have a poorer prognosis and are more likely to develop this cancer than females. A predisposition and environmental factors have a minor role in the genetics that affect the development of ALL. Children with Trisomy 21, Down Syndrome, are at a higher risk of being diagnosed with either myeloid or lymphoid leukemias (Madhusoodhan et al., 2016). Children with Li- Fraumeni syndrome are also at a higher risk of developing leukemia. Li- Fraumeni syndrome has a mutation in the *TP53* gene in germ cells, while hypodiploid ALL is associated with mutations in the *TP53* gene in both the somatic and germ cells (Madhusoodhan, 2016). Some other syndromes which put children at a higher risk of developing ALL are Fanconi's anemia, Bloom Syndrome, and Nijmegen breakage syndrome

(Madhusoodhan et al., 2016). These diseases affect DNA repair in cells. Recent genome studies have found that polymorphisms in single nucleotides have increased the risk of developing ALL. Although there were these findings, they do not count for every single case of pediatric acute lymphoblastic leukemia. Genetic mutations and silencing affect the prognosis of cancer positively or negatively, as well as many other factors such as age, sex, and white blood cell count.

Acute myeloid leukemia (AML) affects 13% of children under ten years old, and unlike ALL, AML develops in the second stage of life. AML accounts for 36% of leukemia cancers from ages 15 to 19 (Madhusoodhan, 2016). Also, unlike ALL, AML affects males and females equally in all age groups. Although AML and ALL can develop without an underlying condition, many different diseases and syndromes can help lead to the development of AML. Like ALL, Fanconi's anemia and Trisomy 21 can lead to AML, but unlike ALL, dyskeratosis congentia, Schwachman-Diamond's syndrome, and Kostmann's syndrome can also lead to AML. Children with Trisomy 21 develop a myeloproliferative disorder linked to mutations in the *GATA1* gene (Madhusoodhan et al., 2016). This gene is an essential transcriptional factor in hematopoiesis. These cases typically regress, while another 20% lead to the development of AML (Madhusoodhan et al., 2016). Many other genetic factors can lead to the development of AML.

Chronic Myeloid Leukemia (CML) is extremely rare in children under twenty years old and mainly affects children over ten years old. This disease is biologically equivalent to the adult version of CML. Pediatric and adult CML has a similar break in the *BCR* gene and creates a *BCR-ABL* fusion (Madhusoodhan et al., 2016). The fusion leads to tyrosine kinase activation, leading to an advantage of the Ph+stem cell clone to duplicate unchecked.

With current studies, society can understand that genetics influences cancer development. Furthermore, we have developed technology that can "cure" cancer at the molecular level, so therapies are more targeted for individual cases.

Recent Progress

Cancer therapies were almost nonexistent until the mid-1900s, when Farber helped develop one of the earliest forms of medicines for leukemia. Since then, more chemotherapies, radiation, and hematopoietic stem cell replacement has been developed to treat cancer. As a result, in recent years, the survival rate in ALL has risen to nearly 80%, while the survival rate for AML and other leukemias has stayed low (Yongshu et al., 2022). Most current therapies include nucleic acid and genetic therapy using natural killer cells. With the advancements in genetics, these therapies are more targeted to individual cases. Nucleic acid therapy has developed many different drugs, such as Fomivirsen, Mipomersen, Inotersen, and many other drugs approved by the FDA for cancer patients (Yongshu et al., 2022). These medications target gene expression, unlike chemotherapies which target protein expression. The targeting of gene expression ultimately improves the disease.

With ALL, scientists have discovered treatments to reduce side effects and recurrence in these children with nucleic acid therapy. In addition, these scientists have discovered, with gene knockdown, that cells can die through apoptosis. Gene knockdown is the process of temporarily stopping or decreasing gene expression. For example, with research, scientists have discovered that the knockdown of the *GPSM1* gene can lead to ALL B-cell cell death by the *ADCY6-RAPGEF3-JNK* signaling pathway (Yongshu et al., 2022). Also, the knockdown of the gene *CREB* can inhibit cell growth and induces apoptosis of pre-B ALL cells. The knockdown of the gene *USP1* induces apoptosis and inhibits cell growth by inhibiting

the ID1/AKT signaling pathway (Yongshu et al., 2022). These processes all inhibit cell growth or induce apoptosis for pre-B or B ALL cells, but there is a way in which the knockdown of a gene where the T ALL cells are stunted in their growth or killed altogether (Yongshu et al., 2022).

Genetic therapy using natural killer (NK) cells is used in targeting both ALL and AML cells. In addition, the immune system uses NK cells with cytotoxic properties, which can be used with genetic engineering to target cancer cells. The treatment of T-cell adoptive transfer is one of the treatments with great success for patients with ALL. Although this treatment has been proven to put patients in remission within three months with a success rate of 81%, some side effects must be taken seriously (Rahnama et al., 2022). Some side effects include developing CAR-associated Hemophagocytic Lymphohistiocytosis, Cytokine Release Syndrome, and Immune Effector Cell Associated Neurotoxicity Syndrome (Rahnama et al., 2022). Furthermore, NK cell therapy has other challenges when used in a clinical setting. NK cells have a short half-life of seven to ten days, and it is hard to get into the tumor environment and get past the tumor's immune defenses (Rahnama et al., 2022). Although this treatment has many opposing sides, the NK cells are more targeted for the patient's case. In addition, the NK cells are now modified using viral factors to improve the challenges of using these cells. There has also been the use of nonviral genetic engineering by using electroporation (Rahnama et al., 2022). This technique makes holes in the NK cells using small pulses of electricity, where it can introduce nucleotides into the cells.

The treatment for Chronic Myeloid Leukemia (CML) has changed drastically through the years, and now tyrosine kinase inhibitor (TKI) has changed how this disease is managed (Madhusoodhan et al., 2016). Imatinib successfully treats CML, although patients may become resistant to the medication. They can become resistant through mutations that affect the binding of the medication and the *BCR-ABL* kinase (Madhusoodhan et al., 2016). In addition, the patients can become resistant to the drug's pharmacokinetics, increasing the efflux of medicine out of the tumor cell. In order to beat this resistance, second-generation drugs such as dasatinib or nilotinib can be used (Madhusoodhan et al., 2016). Unfortunately, these drugs only suppress the disease, and bone marrow transplants remain the only "cure" for CML. Although bone marrow transplants seem to be the only cure for CML, patients can stay in remission for years while on TKIs. Some may even be able to wean off this therapy after a while.

Discussion

Although this is a painful disease that affects people of all ages, the science behind discovering ways to treat this disease is fantastic. Researchers have developed techniques using genetics in order to defeat this disease. With these advancements, pediatric leukemia has become a great success story for many patients. Unfortunately, although it is a success story for many, it still kills many children yearly. Scientists now aim to integrate more nucleic acid and genetic therapies to steer away from the conventional tools used. The genetic tools used in modern-day treatments have become vital for cancer and many other genetic disorders, and there are many great success stories. These techniques have revolutionized the world of modern medicine and are now aimed at being a more personalized treatment for everyone in the world. As society progresses, hopefully, more "cures" will be developed for different kinds of cancer, and cancer's underlying causes and genetics will be exposed. Early prevention and testing will help end the reign of this terrible disease.

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