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Pediatric Acute Lymphoblastic Leukemia: A Review

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Background

Every year approximately 3,500 new cases of pediatric Acute Lymphoblastic Leukemia (ALL) are diagnosed.[1] ALL is characterized by an accumulation of immature B or T lymphocytes, known as blasts, in the bone marrow and blood. ALL originates in the bone marrow where hematopoietic stem cells differentiate into either myeloid or lymphoid stem cells. Lymphoid stem cells further convert into immature cells called lymphoblasts, and the lymphoblasts typically further differentiate into mature B or T lymphocytes. Because of the proliferation of immature white blood cells in ALL, normal healthy white blood cells can become crowded out, leading to a variety of possible symptoms. A child with ALL may display signs and symptoms such as bone or joint pain, fever, frequent infections, loss of appetite, fatigue, easy bruising, shortness of breath, swollen lymph nodes (painless lumps in the neck, underarm, groin, or abdomen), and petechiae (small, flat dark spots due to bleeding under the skin).

Approximately 25% of all cancers diagnosed before age 15 are ALL, and ALL comprises 19% of cancers among all patients under age 20.[2] These statistics make ALL the most common pediatric cancer and most frequent cancer-induced cause of death among patients under the age of 20.[3] Despite these grim facts, successful treatment of ALL has undergone remarkable progress within the last 50-60 years. In 1964, survival rates for children with ALL hovered around 10%.[4] Improvements in survival outcomes have continued in the decades since. Analyses from 1975-1979 indicated a 5-year survival rate for childhood and adolescent ALL patients of 56.8%. Subsequent analyses showed 5-year survival rates of 74.9% from 1985-1989 and 83.8% from 1995-1999.[5] Between 1990-1994 1,194 ALL patients died, while 882 died between 1995 and

1999, and 687 died between 2000 and 2005. In the period from 2000-2005, 5-year survival rates rose to 90.4%, representing a towering achievement in medical progress and collaboration within just five decades.[6] Improved risk stratification, personalized chemotherapy, and further post-induction failure treatments promise to further enhance the survival rates of patients.

Incidence

According to Ward et al. males are diagnosed at a higher rate than females (38.4 for males and 30.2 for females where all rates are given per 1,000,000). ALL is more commonly diagnosed in highly industrialized nations, where there is a spike in ALL incidence rates between ages 2-4. However, the spike is much more pronounced in non-Hispanic white and Hispanic children than black children (about 110 for Hispanics, 105 for whites, and 40 for blacks). Hispanics are diagnosed at the highest rates altogether, followed by non-Hispanic whites, Asians and Pacific Islanders, and non-Hispanic blacks (rates are 44.9, 34.2, 28.7, and 18.3, respectively). Though less black children are diagnosed with ALL, disparities in survival rates have long been documented. From 1980-1984 the 5-year survival rate disparity between whites and blacks was a 21% difference (68% survival for whites, 47% for blacks). However, this disparity has decreased sharply over the last few decades to a 6% difference in survival from 2003-2009 (90% for white, 84% for blacks).[7] This disparity may have to do with blacks having elevated incidence rates of T-cell based ALL, which is considered a high-risk feature relative to B-cell precursor ALL. One favorable prognostic indicator of ALL is hyperdiploidy, which is found in low frequencies in black Americans.[8] A study by Hunger et al. of the Children's Oncology Group (COG) reported that during the period from 2000-2005, 44.5% of blacks had

NCI (National Cancer Institute) high-risk classification group features while just 32.9% of non-Hispanic whites had NCI high-risk classification features. Hispanics were at a 1.5x higher risk of death than non-Hispanics during the period studied.[6] This is likely a result of much higher incidences of particular genomic aberrations in leukemic cells among Hispanics enrolled in COG ALL trials.[9] The reason for higher rates of total incidence in Hispanic populations is currently unknown. Recent studies have examined genetic susceptibility, increasing trends in obesity among Hispanics, and disproportionate exposure to household chemicals.[10]

Risk Stratification

ALL is a model disease for the utilization of risk-based therapy, and the risk of treatment failure determines stratification of treatment intensity. There are several key identifying features of ALL that affect classification and prognosis. Patients with less debilitating features are treated with less toxic regimens, and conversely, those with profiles of higher-risk disease receive more aggressive treatment regimens.[11] In relatively recent years, a renewed emphasis has been placed on identifying the features that routinely affect prognosis. In 1993, the NCI sponsored a workshop in order to define the criteria for risk-based stratification treatment. Workshop participants included physicians and scientists from the COG, Pediatric Oncology Group, Dana-Farber Cancer Institute, and St. Jude Children's Research Hospital. Based on ALL clinical trials and data outcomes of different groups, the NCI group concluded that B-cell precursor patients (which make up the vast majority of ALL patients) between ages 1-10 with a presenting white blood cell (WBC) count at diagnosis of less than 50,000 cells/microliter would comprise the standard-risk category.[12] All other patients are classified into the high-risk ALL group (namely

those less than 1 year of age, older than 10 years of age, or with an initial WBC greater than 50,000 cells/microliter). Additionally, patients taking corticosteroids prior to their diagnostic blood workup are automatically considered high-risk due to the confounding effects of steroids on WBC count.[11]

Different conclusions have resulted from different treatment strategies for T-cell ALL, and consequently, some institutions automatically label these patients as high risk while other institutions continue to rely on classification by age and WBC count for T-cell patients. Hunger et al. found that among 21,626 children and adolescents from 1990-2005, patients with T-cell ALL had a higher risk of death than patients with B-cell ALL. Additionally, patients classified as NCI high risk ALL individuals had a 2.4-3.6 fold increased risk of death when compared with NCI standard risk patients.[6] Overall, there is consensus that by improving the uniformity of risk stratification based therapy, the efficiency of forthcoming ALL research will also improve.

Genetics

Conventionally, the NCI risk stratification features of patient age and WBC count at diagnosis have shown the most consistent predictive power. However, numerous other clinical and biologic factors have been scrutinized for prognostic value, though few remain after multivariate analysis.[13] Leukemic cell chromosomal number has been one of the factors to routinely appear prognostic, with some research suggesting that the presence of additional specific chromosomes may be more noteworthy than a general increase in total ploidy. There are also several genetic abnormalities that are associated with better or worse outcomes. However, there is generally no consensus on how to incorporate many of the more specific and novel

genetic component findings of the disease into high or standard-risk stratification groups, and this is due in part to the relatively recent advent of genome-wide analysis of patients which is necessary to find these potentially prognostic genetic profiles.[14] This lack of consensus can be further attributed to inconsistent findings among clinical trial groups when modifying treatment plans for a specific genetic abnormality. Distinct genetic irregularities are identified in approximately 75-80% of pediatric ALL cases with typical chromosomal and molecular genetic analyses, but through the use of genome-wide analysis, genetic abnormalities are found in virtually all cases.[14] Beyond specific mutations in genes that regulate different hematopoietic aspects, two well-documented genetic anomalies associated with better or worse outcomes are hypodiploidy and hyperdiploidy. Hyperdiploidy has been associated with favorable outcomes, while hypodiploidy is strongly associated with poor outcomes.

Hyperdiploidy

In about 20-25% of B-cell precursor ALL, patients present with high hyperdiploidy (defined as 51 to 65 chromosomes per leukemic cell or a DNA index of greater than 1.16).[11] DNA index is a prognostic factor used specifically in childhood ALL which measures the chromosomal material of cancerous cells.[15] In 2005, Sutcliffe et al. published a paper in which two independent groups, the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG), examined the significance of three specific trisomies (a type of chromosomal abnormality in which there are three copies of a particular chromosome instead of the usual two). The two groups both analyzed populations of patients with NCI standard and high-risk stratification classifications. A total of 5,484 patients were analyzed (1,582 by the CCG and

3,902 by the POG), and eight-year event free survival rates (EFS) of 91% (CCG) and 89% (POG) were reported in patients assigned to the standard risk classification groups whose leukemic cells had concurrent trisomies of chromosomes 4, 10, and 17. Further analysis from the POG showed that hyperdiploidy in general was less of a significant favorable prognostic factor without the three crucial trisomies, and this finding supports the conclusions of previous POG and CCG studies in which results indicated that specific trisomies hold more favorable prognostic weight than general chromosome number for predicting outcome in the same patient type (pediatric B-precursor ALL patients).[16] For the NCI high-risk classification patients from the sample population, no prognostic significance was found regarding the number of agreeable trisomies.[17]

Hypodiploidy

Hypodiploidy (defined as having a modal leukemic cell chromosomal number below 46 or a DNA index of less than 0.81) has been found to be strongly associated with poor outcomes in pediatric ALL patients. Nachman et al. analyzed data on 139 hypodiploid patient cases gathered from 10 different cooperative groups and institutions. Patients were grouped based on chromosomal number of leukemic cells and 4 categories resulted: 24-29 chromosomes (n=46), 33-39 chromosomes (n=13), 40-43 chromosomes (n=13), and 44 chromosomes (n=54). Again, eight-year EFS rates were analyzed and determined to be just 38.5% ± 4.4% overall. No substantial differences were found in outcomes for patients from the 24-29, 33-39, or 40-43 chromosome groups, but the 44 chromosome group independently had eight-year EFS rates of 52.2% compared to 30.1% for the remaining three groups collectively. Patients in the 44

chromosome group had worse EFS rates if they had a monosomy 7, dicentric chromosome (an abnormality in which a chromosome has two centromeres), or both.[18] Though hypodiploid patients with 45 chromosomes in their leukemic cells were not analyzed in the previously discussed study, they have been shown to have significantly better outcomes than those hypodiploid patients with less than 45 chromosomes in their leukemic cells.[19]

Treatment

Response to initial treatment therapy is also considered to be an especially reliable and independent prognostic indicator. Remission induction is the goal of the first of three major components of treatment in recently diagnosed ALL patients (some publications consider there to be four major components, and all four aspects will be discussed). Complete remission (the goal of induction) is usually defined to mean that less than 5% of immature blast cells remain in a patient's bone marrow, and the vast majority of patients achieve this initial milestone.

Induction

According to pediatric hematology oncology physicians Stacy Cooper and Patrick Brown, induction therapy typically lasts 4-6 weeks and consists of chemotherapy with the drugs vincristine, anthracycline (doxorubicin or daunorubicin), asparaginase, and corticosteroids (prednisone or dexamethasone). Patients are typically admitted to the hospital before beginning treatment, but barring any complications, patients may be discharged and continue treatment as outpatients. Severe infections are more likely during this phase of treatment.[11] Additionally,

relapse has been shown to occur universally without additional treatment, necessitating the subsequent two phases.[20]

Consolidation

In those that successfully achieve remission, the next treatment phase is known as consolidation and aims to further reduce the presence of leukemic cells throughout the body. This phase lasts about 6-9 months but is dependent upon risk classification of the patient and which specific cancer group's protocol is being followed. Consolidation generally occurs in an outpatient setting. Those patients with higher-risk classifications would typically receive longer and stronger drug regimens. Some of the primary chemotherapeutic drugs used are mercaptopurine, thioguanine, methotrexate, cyclophosphamide, etoposide, and cytarbine. These drugs differ from those of the induction phase and are used in certain combinations to improve collective effectiveness and reduce drug resistance. Higher risk patients may receive a second burst of intense chemotherapy within the consolidation phase known as delayed intensification.[11]

Maintenance

If the patient remains in remission after both the induction and consolidation phases, then the final and longest phase of treatment can commence, known as maintenance. Maintenance is significantly longer and less intense than the prior two phases and has been demonstrated to reduce the risk of relapse after remission has been achieved.[11] However, the precise explanations for why maintenance is a necessary phase and the most effective composition of maintenance

have yet to be fully elucidated.[20] Furthermore, due to the extensive length (2-3 years) and daily requirements of the phase, there are issues with patient adherence. Approximately 20% of patients are less than 90% adherent, and unfortunately adherence of less than 90% is associated with a relapse risk four times higher than patients who are over 90% adherent.[21] Maintenance treatment is based primarily around antimetabolite therapy with the drugs methotrexate (weekly, oral) and mercaptopurine or thioguanine (daily, oral).[11] Individual metabolic differences are becoming increasingly notable in how they affect the use of these drugs during maintenance.

Intrathecal Therapy

As previously mentioned, some publications consider there to be a fourth phase of standard treatment which involves therapy directed specifically against the central nervous system (CNS). Three different methods can be utilized to expunge signs of disease from the CNS, and these include cranial irradiation, systemic chemotherapy capable of penetrating the blood-brain barrier, and direct intrathecal chemotherapy administration. Most treatment groups begin using intrathecal chemotherapy upon induction of remission. Other groups use protocols using intrathecal therapy throughout the treatment process while others do not utilize it during the maintenance phase.[11] During the 1960s and 1970s, cranial irradiation drastically increased cure rates in ALL patients. However, it was associated with some increased risk of secondary CNS tumors and neurocognitive effects, particularly with younger patients.[22] For these reasons the use of cranial irradiation has been progressively declining, and it is generally reserved for those patients with the highest risk of CNS relapse. Multiple research groups have implemented treatment protocols eliminating CNS irradiation entirely for almost all newly diagnosed patients

and have seen results similar to those reported by research groups who continue to use irradiation treatment. The use of cranial irradiation remains controversial, but currently all research groups treat approximately 80% of pediatric patients without CNS irradiation.[23]

Treatment Failure

Induction failure and relapse are the primary avenues by which treatment may fail. Relapse is more common and has experienced little progress in treatment strategies in contrast with the increasingly improving outcomes of newly diagnosed ALL patients.[24] Though induction failure is rarer, it portends more unfavorable outcomes.

Induction Failure

Cooper and Brown report that failure to reach remission after initial induction therapy occurs in 3-5% of pediatric ALL patients and forebodes a particularly dismal prognosis – approximately 33% overall survival (OS) rates, making induction failure one of the most unfavorable possible outcomes during pediatric ALL treatment.[11] About 95% of patients do reach this important prognostic benchmark of initial complete remission, but for those who do not, risk stratification promptly changes. Due to the rarity of induction failure, those who do not achieve remission are almost always reclassified into a third risk subgroup, very-high-risk. A study by Schrappe et al. examined data from 14 different study groups on 44,017 patients between the ages of 0-18 who were recently diagnosed with ALL and had begun treatment. 1,041 of the total patients experienced induction failure. The study defined induction failure as

leukemic blast persistence in the bone marrow, blood, or any extramedullary location between 28 and 43 days after beginning treatment. Various treatment strategies were employed for induction failure patients among the study groups analyzed. Treatments utilized included additional chemotherapy, clinical trial enrollment, and hematopoietic stem cell transplantation (HSCT). The primary conclusion upon statistical analysis of outcomes and patient data is that there is tremendous clinical and biologic heterogeneity among patients who experience induction failure.[25]

Relapsed Disease

Of those who successfully complete induction therapy and advance to further treatment phases, approximately 15-20% of ALL patients experience relapsed disease, and cure rates are significantly lower following relapse.[26] Relapse is the most common cause of treatment failure, and like newly diagnosed patients, relapsed ALL patients are risk stratified. Stratification now depends primarily upon the length of the first remission and the location of relapse within the body (marrow relapses are the most common). Cooper and Brown report that late relapses occurring greater than three years after diagnosis have the best prognosis, while relapses between 18-36 months are given an intermediate prognosis, and those within 18 months of diagnosis have the worst outcomes.[11] HSCT is used in greater than 50% of relapsed patients, but there are multiple different treatment strategies, again depending on which treatment group's care the patient is under.[27] There has been a greater influx in recent years of research investigating the biology of relapse, antibody-based therapies, and other immunological approaches.[24]

New Treatments and the Optimistic Future of ALL

Blinatumomab and chimeric antigen receptor (CAR) T cell therapy are two new innovative immunotherapies that have demonstrated success in treating patients with relapsed or refractory ALL. Refractory patients are typically defined as those patients that have relapsed and had a second round of additional therapy fail as well. Advances in genomic technology and personalized medicine also show promise in the future treatment of ALL.

Blinatumomab

Blinatumomab (a monoclonal antibody) is a bispecific T-cell engager (BiTE) that exerts its effect by facilitating interaction between a patient's own T and B cells. Blinatumomab contains binding sites for two distinct targets: the CD19 antigen on B cells and the CD3 site on T cells. By linking both of these cell types, blinatumomab facilitates the activation and production of cytotoxic effects by T cells. The drug binds to both benign and malignant cells of B-lineage origin. Lysis of CD19-positive cells is directed by the proliferation of T cells and release of inflammatory cytokines and cytolytic proteins.[28,29]

In 2016, von Stackelberg et al. published the results of a Phase I/Phase II clinical trial of blinatumomab in pediatric patients who had relapsed or refractory ALL. The study was the first of its kind in pediatrics and evaluated the safety, pharmacokinetics, recommended dosage, and potential for efficacy of the drug. 49 patients (all under the age of 18) were treated in phase I and a recommended dosage was determined. 44 patients were treated in phase II, and a total of 70 received the recommended dosage. 27 patients achieved complete remission (CR) within the first

two cycles of drug administration. However, at the end of a 2-year follow-up, of the 27 who achieved CR 4 were still in remission. Two had relapsed but were alive, three had withdrawn consent, three died in CR after receiving HSCT, and fifteen had relapsed and died. Further investigation of blinatumomab is supported based upon the anti-leukemic activity of the drug.[30]

CAR-T Cell Therapy

On August 30th, 2017, tisagenlecleucel (CD19 directed CAR-T cell therapy) was approved by the FDA for certain pediatric and young adult cancer patients, making it the first gene therapy available in the United States. This therapy works by genetically modifying a patient's own T-cells so that they can locate and destroy cancerous B cells. The T cells are removed from the patient, mailed to a manufacturing center, and genetically altered so that they are able to display a specific receptor (a chimeric antigen receptor, or CAR). The cells are then infused back into the patient. The CAR receptors on the modified T cells direct them to bind to and kill B cells displaying the CD19 antigen.[31] A phase I/II study of CAR-T cell therapy conducted by the Children's Hospital of Philadelphia and the University of Pennsylvania showed a CR rate of 90% among 30 children with relapsed or refractory ALL.[32] In 2018, a second comprehensive study of tisagenlecleucel was conducted. The phase II clinical trial was a global, 25 center collaborative study conducted in relapsed or refractory ALL patients between the ages of 3 and 21. 75 patients received treatment, and the overall remission rate was 81% while 45 patients attained complete remission. The rates of OS and EFS were 90% and 73% respectively at 6 months and 76% and 50% at 12 months. There are substantial, though primarily transient, risks associated with the therapy, namely cytokine release syndrome (CKS).[33] High fever can

result from CKS, and in some situations can progress to respiratory and cardiovascular compromise. However, there has been success in treating CKS with the drugs etanercept and tocilizumab.[34] Overall, the use of tisagenlecleucel resulted in high remission rates, and though side effects can be severe, they can be mitigated in most patients.

Genome-wide Analysis

Partly in response to the tremendous heterogeneity of patients who experience treatment failure, whether it be through relapse or induction failure, there has been a significant amount of ALL research focusing on the identification of genetic alterations and the development of new classification subtypes. Recent research with genome-wide analysis has also identified clinically relevant and novel genetic abnormalities that could serve as treatment targets. These advances in biomedical technology are a promising sign of the legitimacy of personalized treatment plans maximizing drug effectiveness and minimizing toxicity based individually on distinct genetic profiles.[35]

Acute Lymphoblastic Leukemia has become a representative success story of the triumphs of modern medicine. Before 1960, for the vast majority of patients a diagnosis of ALL was essentially a death sentence. Survival rates hovered around an abysmal 10%, and thousands of children died every year from the disease. Today, overall survival rates for newly diagnosed patients are approximately 90%. This sharp contrast can be attributed to the relentless pursuit of research on treatments and the different profiles in which the disease manifests. The development of chemotherapeutic agents and the elucidation of the optimal administration of these agents have presumably afforded many thousands of children the opportunity to live out

their lives. Unfortunately, many patients still die from ALL and its complications, but continued research, innovation, and advances in immunotherapy, genomics, and personalized medicine provide legitimate reason for optimism about the future outlook of ALL patients who have experienced treatment failure. It is not unforeseeable that a day could soon arise when using high throughput genomic sequencing, chemotherapy, immunotherapy, and personalized treatment plans that all patients could have a legitimate chance of cure.

References

1. Inaba, H., Greaves, M., & Mullighan, C. G. (2013). Acute lymphoblastic leukaemia. *The Lancet*, *381*(9881), 1943-1955.
2. Ries, L. A. G., Smith, M. A., Gurney, J. G., Linet, M., Tamra, T., Young, J. L., & Bunin, G. (1999). Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. *Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995*.
3. Smith, M. A., Seibel, N. L., Altekruse, S. F., Ries, L. A., Melbert, D. L., O'Leary, M., ... & Reaman, G. H. (2010). Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *Journal of Clinical Oncology*, *28*(15), 2625.
4. Pierce, M. I., Borges, W. H., Heyn, R., Wolff, J. A., & Gilbert, E. S. (1969). Epidemiological factors and survival experience in 1770 children with acute leukemia treated by members of Children's Study Group A between 1957 and 1964. *Cancer*, *23*(6), 1296-1304.
5. Linabery, A. M., & Ross, J. A. (2008). Childhood and adolescent cancer survival in the US by race and ethnicity for the diagnostic period 1975-1999. *Cancer*, *113*(9), 2575-2596.
6. Hunger, S. P., Lu, X., Devidas, M., Camitta, B. M., Gaynon, P. S., Winick, N. J., ... & Carroll, W. L. (2012). Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *Journal of Clinical Oncology*, *30*(14), 1663.
7. Ward, E., DeSantis, C., Robbins, A., Kohler, B., & Jemal, A. (2014). Childhood and adolescent cancer statistics, 2014. *CA: A Cancer Journal for Clinicians*, *64*(2), 83-103.
8. Pollock, B. H., DeBaun, M. R., Camitta, B. M., Shuster, J. J., Ravindranath, Y., Pullen, D. J., ... & Murphy, S. B. (2000). Racial differences in the survival of childhood B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group Study. *Journal of Clinical Oncology*, *18*(4), 813-823.
9. Harvey, R. C., Mullighan, C. G., Chen, I. M., Wharton, W., Mikhail, F. M., Carroll, A. J., ... & Carroll, W. L. (2010). Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. *Blood*, *115*(26), 5312-5321.
10. Giddings, B. M., Whitehead, T. P., Metayer, C., & Miller, M. D. (2016). Childhood leukemia incidence in California: high and rising in the Hispanic population. *Cancer*, *122*(18), 2867-2875.
11. Cooper, S. L., & Brown, P. A. (2015). Treatment of pediatric acute lymphoblastic leukemia. *Pediatric Clinics*, *62*(1), 61-73.
12. Smith, M., Arthur, D., Camitta, B., Carroll, A. J., Crist, W., Gaynon, P., ... & Murphy, S. (1996). Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *Journal of Clinical Oncology*, *14*(1), 18-24.
13. Donadieu, J., Auclerc, M. F., Baruchel, A., Leblanc, T., Landman-Parker, J., Perel, Y., ... & Leverger, G. (1998). Critical study of prognostic factors in childhood acute lymphoblastic leukaemia: differences in outcome are poorly explained by the most significant prognostic variables. *British Journal of Haematology*, *102*(3), 729-739.
14. Pui, C. H., Carroll, W. L., Meshinchi, S., & Arceci, R. J. (2011). Biology, risk stratification, and therapy of pediatric acute leukemias: an update. *Journal of Clinical Oncology*, *29*(5), 551.
15. Rachieru-Sourisseau, P., Baranger, L., Dastugue, N., Robert, A., Geneviève, F., Kuhlein, E., & Chassevent, A. (2010). DNA Index in childhood acute lymphoblastic leukaemia: a karyotypic method to validate the flow cytometric measurement. *International Journal of Laboratory Hematology*, *32*(3), 288-298.
16. Harris, M. B., Shuster, J. J., Carroll, A., Look, A. T., Borowitz, M. J., Crist, W. M., ... & Land, V. J. (1992). Trisomy of leukemic cell chromosomes 4 and 10 identifies children with B-progenitor cell acute lymphoblastic leukemia with a very low risk of treatment failure: a Pediatric Oncology Group study. *Blood*, *79*(12), 3316-3324.
17. Sutcliffe, M. J., Shuster, J. J., Sather, H. N., Camitta, B. M., Pullen, J., Schultz, K. R., ... & Heerema, N. A. (2005). High concordance from independent studies by the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) associating favorable prognosis with combined trisomies 4, 10, and 17 in children with NCI Standard-Risk B-precursor Acute Lymphoblastic Leukemia: a Children's Oncology Group (COG) initiative. *Leukemia*, *19*(5), 734.

18. Nachman, J. B., Heerema, N. A., Sather, H., Camitta, B., Forestier, E., Harrison, C. J., ... & Silverman, L. B. (2007). Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia. *Blood*, *110*(4), 1112-1115.
19. Harrison, C. J., Moorman, A. V., Broadfield, Z. J., Cheung, K. L., Harris, R. L., Reza Jalali, G., ... & Eden, T. O. (2004). Three distinct subgroups of hypodiploidy in acute lymphoblastic leukaemia. *British Journal of Haematology*, *125*(5), 552-559.
20. Hunger, S. P., & Mullighan, C. G. (2015). Acute lymphoblastic leukemia in children. *New England Journal of Medicine*, *373*(16), 1541-1552.
21. Bhatia, S., Landier, W., Hageman, L., Kim, H., Chen, Y., Crews, K. R., ... & Maloney, K. W. (2014). 6MP adherence in a multiracial cohort of children with acute lymphoblastic leukemia: A Children's Oncology Group Study. *Blood*, *124*(15), 2345-2353.
22. Krull, K. R., Brinkman, T. M., Li, C., Armstrong, G. T., Ness, K. K., Srivastava, D. K., ... & Robison, L. L. (2013). Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: a report from the St Jude lifetime cohort study. *Journal of Clinical Oncology*, *31*(35), 4407.
23. Pui, C. H., Campana, D., Pei, D., Bowman, W. P., Sandlund, J. T., Kaste, S. C., ... & Coustan-Smith, E. (2009). Treating childhood acute lymphoblastic leukemia without cranial irradiation. *New England Journal of Medicine*, *360*(26), 2730-2741.
24. Bhojwani, D., & Pui, C. H. (2013). Relapsed childhood acute lymphoblastic leukaemia. *The Lancet Oncology*, *14*(6), e205-e217.
25. Schrappe, M., Hunger, S. P., Pui, C. H., Saha, V., Gaynon, P. S., Baruchel, A., ... & Escherich, G. (2012). Outcomes after induction failure in childhood acute lymphoblastic leukemia. *New England Journal of Medicine*, *366*(15), 1371-1381.
26. Nguyen, K., Devidas, M., Cheng, S. C., La, M., Raetz, E. A., Carroll, W. L., ... & Loh, M. L. (2008). Factors influencing survival after relapse from acute lymphoblastic leukemia: A Children's Oncology Group Study. *Leukemia*, *22*(12), 2142.
27. Peters, C., Schrappe, M., von Stackelberg, A., Schrauder, A., Bader, P., Ebell, W., ... & Ehlert, K. (2015). Stem-cell transplantation in children with acute lymphoblastic leukemia: a prospective international multicenter trial comparing sibling donors with matched unrelated donors-The ALL-SCT-BFM-2003 trial. *Journal of Clinical Oncology*, *33*(11), 1265-1274.
28. Dreier, T., Lorenczewski, G., Brandl, C., Hoffmann, P., Syring, U., Hanakam, F., ... & Baeuerle, P. A. (2002). Extremely potent, rapid and costimulation-independent cytotoxic T-cell response against lymphoma cells catalyzed by a single-chain bispecific antibody. *International Journal of Cancer*, *100*(6), 690-697.
29. Hoffmann, P., Hofmeister, R., Brischwein, K., Brandl, C., Crommer, S., Bargou, R., ... & Baeuerle, P. A. (2005). Serial killing of tumor cells by cytotoxic T cells redirected with a CD19-/CD3-bispecific single-chain antibody construct. *International Journal of Cancer*, *115*(1), 98-104.
30. von Stackelberg, A., Locatelli, F., Zugmaier, G., Handgretinger, R., Trippett, T. M., Rizzari, C., ... & Schlegel, P. G. (2016). Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *Journal of Clinical Oncology*, *34*(36), 4381-4389.
31. Kalos, M., Levine, B. L., Porter, D. L., Katz, S., Grupp, S. A., Bagg, A., & June, C. H. (2011). T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. *Science Translational Medicine*, *3*(95), 95ra73-95ra73.
32. Maude, S. L., Frey, N., Shaw, P. A., Aplenc, R., Barrett, D. M., Bunin, N. J., ... & Mahnke, Y. D. (2014). Chimeric antigen receptor T cells for sustained remissions in leukemia. *New England Journal of Medicine*, *371*(16), 1507-1517.
33. Maude, S. L., Laetsch, T. W., Buechner, J., Rives, S., Boyer, M., Bittencourt, H., ... & Qayed, M. (2018). Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *New England Journal of Medicine*, *378*(5), 439-448.
34. Grupp, S. A., Kalos, M., Barrett, D., Aplenc, R., Porter, D. L., Rheingold, S. R., ... & Milone, M. C. (2013). Chimeric antigen receptor–modified T cells for acute lymphoid leukemia. *New England Journal of Medicine*, *368*(16), 1509-1518.
35. Pui, C. H., Mullighan, C. G., Evans, W. E., & Relling, M. V. (2012). Pediatric acute lymphoblastic leukemia: where are we going and how do we get there?. *Blood*, *120*(6), 1165-1174.