J Cancer Immunol. 2024;6(2):70-76.

Journal of Cancer Immunology Mini Review

Tertiary Prevention and Treatment for Reducing Leukemia Relapse

Nikita Manyak[1], Mingyi Chen MD, PhD[2], Su Yon Jung PhD[3,*]

[1]School of Nursing, University of California, Los Angeles, Los Angeles, CA, USA

[2]Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA

[3]Translational Sciences Section, School of Nursing, Department of Epidemiology, Fielding School of Public Health, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles, CA, USA

[*]Correspondence should be addressed to Su Yon Jung, sjung@sonnet.ucla.edu

Received date: March 28, 2024, **Accepted date:** July 07, 2024

Citation: Manyak N, Chen M, Jung SY. Tertiary Prevention and Treatment for Reducing Leukemia Relapse. J Cancer Immunol. 2024;6(2):70-76.

Abstract

We have found little available information in the medical literature on the prevention and treatment of tertiary leukemia or patients' prognosis. We thus conducted a comprehensive literature review using the most recently updated American Society of Hematology guidelines, searching the MEDLINE and PubMed electronic databases by using the key term "progression-free survival (PFS) leukemia" and restricting results to the English language within the last decade. From the initially identified 1,083 papers, we extracted relevant data and treatment recommendations for leukemia patients. Standard treatments like Daunorubicin, Doxorubicin, and Asparaginase for children, adolescents, and young adults (18 to 24 years) have high relapse and complication rates within 5 years of treatment. Blinatumomab and Ibrutinib-Rituximab have higher success rates in PFS and a greater overall survival rate than other chemotherapy options have. Two-year disease-free survival was 39.0% with intensive chemotherapy, whereas it rose to 54.4% with anticancer drugs. Additionally, patients who underwent radiotherapy after relapse exhibited better long-term prevention of another relapse and a higher overall survival rate of 77.7% compared with 11.3% in patients not treated with radiotherapy. In the realm of pediatric leukemias, allogeneic stem cell treatments stand out as the most effective, boasting a superior remission rate. Notably, Tisagenlecleucel, a chimeric antigen receptor (CAR) T-cell therapy, is approved for managing relapses of pediatric leukemias after initial or tertiary remission, with a promising 50% survival rate over 5 or 10 years. Further study on immunotherapies is warranted across diverse age groups from a tertiary prevention perspective.

Keywords: Leukemia, Prevention, Survival, Relapse, Children, Young adults, Immunotherapy, CAR T-cell therapy, ASH guidelines

Introduction

Leukemia is an umbrella term for several different cancers of the blood and the blood-forming tissues such as bone marrow. It causes large numbers of abnormal blood cells to be produced and enter the bloodstream. Acute leukemia arises owing to a succession of genetic alterations within a precursor cell in the hematopoietic lineage, leading to the formation of leukemia-initiating cells. These genetic modifications disrupt the typical growth and differentiation processes of hematopoietic cells, leading to excessive accumulation of abnormal immature cells and blasts in both the bone marrow and circulating blood. Most general practitioners have encountered cases of chronic lymphocytic, acute lymphoblastic, chronic myelogenous, and acute myelogenous leukemias in both sexes and various age groups in their clinical experience [1]. Common risk factors for these diseases include genetic predisposition and environmental factors such as exposure to ionizing radiation [1]. The risk of leukemia varies among populations of different ages, sexes, and geographical locations [2]. The observed discrepancies may stem from variations in the frequency of distinct environmental and genetic risk factors associated with leukemia. Some congenital disorders, such as Down syndrome and Fanconi anemia are associated with an increased risk of leukemia. Also, prior exposure to certain chemicals such as benzene, smoking, and air pollution, as well as exposure to radiation and chemotherapy, increases the risk of leukemia development. A two-hit hypothesis for the development of B lymphoblastic leukemia/lymphoma includes predisposing genetic mutation and infections [3].

From the perspective of prevention, there are four levels of disease onset and progression: primary, secondary, tertiary, and quaternary [4]. Primary prevention aims to prevent the initiation of illness or injury; examples include immunization to prevent infections associated with the development of leukemia and avoiding exposure to known risk factors, such as certain chemicals or ionizing radiation [4-6]. Secondary prevention emphasizes the timely identification and treatment of a disease or injury in its early, more treatable stages to mitigate the risk of more serious complications arising; examples are regular screening including blood testing for cancer markers, physical exams, scans, or any other testing deemed necessary by the physician [4,7], and monitoring individuals with a family history of leukemia for early signs and symptoms [7]. Tertiary prevention focuses on reducing the effects of the disease once it has been established, rehabilitation after significant illness, and prevention of comorbidity. Some diseases in which tertiary prevention measures are most commonly used are diabetes, with the use of insulin; cardiovascular disease, with the institution of lifestyle changes; and substance abuse, with participation in rehabilitation programs [4,8]. Tertiary prevention of leukemia includes the use of chemotherapy and other treatments aiming for its control or remission, as well as supportive care measures to minimize the side effects of treatment and improve the patient's overall well-being [8]. Quaternary prevention is a more recent practice that focuses on identifying excessive use of medication and protecting patients from continued unnecessary treatment; one example would be when a physician refrains from potentially harmful invasive testing or excessive treatment of a patient with some unexplained symptoms [4,9]. Quaternary prevention of leukemia would include implementing treatment plans that prioritize the patient's quality of life and minimize unnecessary interventions and avoiding aggressive treatments with limited benefit to prevent potential harm [9].

Given the nature of leukemia, it is difficult to follow the standards of each level of prevention perfectly. However, the primary and tertiary levels have been substantially addressed. Prevalent lifestyle and metabolic risk factors linked to the incidence (primary prevention) and mortality (tertiary prevention) of leukemia that can be modified or avoided are smoking, physical inactivity, overweight, obesity, and hypercholesterolemia. In general, the mortality rate associated with leukemia has declined consistently over the last 10 years, possibly attributed to the emergence of new therapeutic approaches and targeted medications. However, in Ecuador, Belarus, Thailand, and the Philippines, the mortality rate has increased, and the incidence of leukemia has also been increasing in Germany, Korea, Japan, Canada, and the United Kingdom [10]. It is recommended that high doses of radiation, exposure to benzene, smoking or other tobacco use, and obesity/obesity-related lifestyles be avoided to decrease one's chances of developing leukemia [11]. Once the diagnosis has been made, however, treatment must be promptly started with routine blood checks and scanning for cancer markers by flow cytometry, cytogenetics, and fluorescence in situ hybridization. In 2020, the American Society of Hematology (ASH) published new evidence-based guidelines to support patients with acute myeloid leukemia (AML) and their health care providers in making treatment decisions [12]. To create these new guidelines and ensure their completeness, ASH had formed a multidisciplinary panel that included both patients and specialists in myeloid leukemia, geriatric oncology, patient-reported outcomes and decision-making, frailty, epidemiology, and methodology.

During an initial review, we found a relative lack of literature pertaining to the tertiary prevention of leukemia, particularly on methods or treatments for reducing the risk of its relapse. Relapse, or recurrence, is when the cancer returns after a period during which it was undetectable or when its signs and symptoms disappeared following treatment [13]. Relapse signifies the survival of cancer cells after initial treatment or the emergence of new cancer cells, which may occur either at the primary site or in a different area of the body [13]. We were particularly interested in researching the period of remission, that time during which the signs and symptoms of cancer are reduced or eliminated [14], and its duration. Remission does not necessarily mean that the cancer cells have entirely been eradicated, but only that the disease is not actively progressing. There are two types of remission, complete and partial [14]. Complete remission, the ideal situation, is when no evidence of cancer can be found and all signs and symptoms have disappeared, whereas in partial remission, only some signs and symptoms have improved or disappeared [14].

In our review on the tertiary prevention of relapse of leukemia after its remission, we wanted to focus on three age groups of patients: children from birth to 12, adolescents from 12 to 18, and young adults from 18 to 24 years old. Among those age groups, acute lymphocytic leukemia and chronic lymphocytic leukemia are the most common forms of the disease. Unfortunately, the data we were able to extract in our review were not age specific, but we are continuing to explore this issue in hopes of getting clarity for future research.

To conduct our extensive systematic review of the literature focusing on the tertiary prevention of leukemia, we searched PubMed and MEDLINE using the key words "progression-free survival leukemia" and narrowed our search by filtering for English language articles published over the last decade. We initially found a total of 1,083 published papers. We then further narrowed our search with filters for clinical trials, meta-analyses, randomized controlled trials, reviews, and systematic reviews. For consistency and to avoid selection bias while still obtaining a complete dataset, we excluded some articles from our analysis for the following reasons: 152 because they did not discuss tertiary prevention, 236 because they did not fit our filters for the type of paper, 184 because they did not discuss the age groups we were studying, and 20 because the results were not promising for patients. Thus, our final review of the literature included 491 papers, from which

we extracted recommendations. In summary, although we had a wealth of information on the topic of leukemia, finding information about tertiary prevention of leukemia proved to be challenging. This review provides an overview of acute and chronic leukocytic leukemia, encompassing its pathogenesis, risk factors, existing treatments, and the assessment of treatment efficacy and failure. Enhanced comprehension of leukemia's underlying mechanisms could pave the way for innovative targeted therapies, ultimately diminishing the prevalence and risk of relapse of leukemia [15].

Results and Discussion

Our review of the literature revealed that the primary treatment for leukemia usually involves systematic therapies aimed at eradicating leukemia cells throughout the body. These treatments include chemotherapy, targeted therapy, immunotherapy, and stem cell transplantation [16]. The choice of treatment depends on the type of leukemia, its subtype, the patient's overall health, and other factors. The evolution of leukemia treatment from chemotherapy and immunotherapy to targeted and individualized therapy has significantly improved patients' survival rate. The ASH guidelines on leukemia were published in 2020 and are intended to help patients and their healthcare providers make critical care decisions including if and how to proceed with cancer treatment and the need for bone marrow transplant. The CAP (College of American Pathologists)–ASH guideline on the initial diagnostic work-up of amyloidosis (AL) was reviewed for development rigor by methodologists. Then, an American Society of Clinical Oncology Endorsement Expert Panel updated the literature search and reviewed the content and recommendations. Key critical outcomes for decision-making were considered for mortality and survival and functional-status impairment. Other outcomes included quality-of-life impairment, severe toxicity, morphologic complete response, burdens on caregivers, hospitalization, major bleeding, recurrence, duration of response, and type of treatment necessary. In 2023, ASH formed a guideline panel to update the 2020 guidelines. The methodology team conducted systematic reviews of new evidence, and the panel will revise previous recommendations.

Standard chemotherapy drugs used for leukemias are normally administered orally or injected. They work by harming the genetic material within the cellular nuclei; some damage the cells during the process of division, and others inflict damage as the cells replicate their genetic material prior to division [17]. In general, standard treatments for leukemias in children, adolescents, and young adults include daunorubicin, doxorubicin, and asparaginase. Daunorubicin is an anthracycline antibiotic that is mainly used to treat acute and chronic leukemias [18]. It inhibits DNA synthesis by binding to nucleic acids and preventing them from assembling into the DNA double helix structure, effectively slowing the growth of cancer cells [18]. Doxorubicin, also an anthracycline, is primarily used in the treatment of soft tissue and bone sarcomas, as well as breast, ovarian, bladder, and thyroid cancers [19]. It functions by inserting itself between DNA strands, interfering with the repair process mediated by topoisomerase-II and initiating the production of free radicals, effectively harming the cellular membranes, DNA, and proteins [19]. Asparaginase is most commonly used to treat lymphoma and acute lymphocytic leukemia [20]. This drug is an enzyme that hydrolyzes asparagine to form nonfunctional aspartic acid and ammonia, thus depriving tumor cells of a required acid and blocking tumor cell proliferation by interrupting asparagine-dependent protein synthesis [20]. In general, these chemotherapies have been linked to significant rates of recurrence and other side effects within 5 years after the start of the treatment [21].

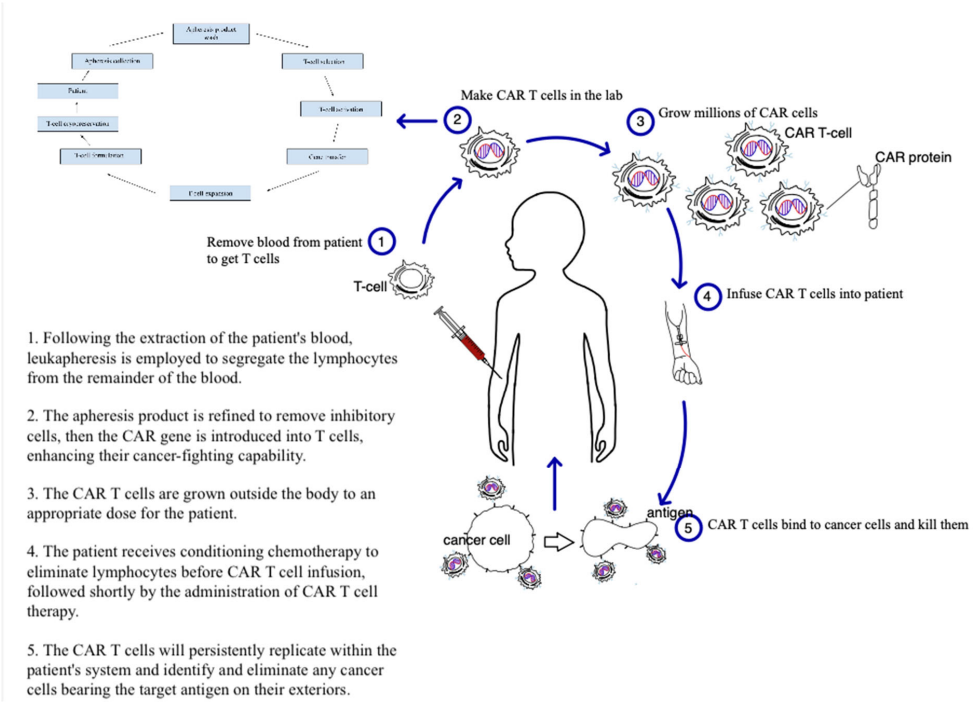
Other anticancer drugs also act against malignant disease; these include alkylating agents, antimetabolites, natural products, and hormonal therapies. For example, blinatumomab is a type of targeted cancer drug called a bispecific monoclonal antibody [22]. This drug works by linking a CD3 site for T cells and a CD19 site for the target B cells, activating the T cells to exert cytotoxic activity on the target cells [22]. Another treatment, ibrutinib–rituximab, is an orally administered covalent inhibitor of Bruton's tyrosine kinase (Btk) that is an active second-line treatment option for patients with chronic lymphocytic leukemia [23,24]. This agent works by forming a covalent bond with CYS-481 at the active site of Btk. It stops the full activation of Btk by inhibiting its autophosphorylation at Tyr-223, leading to the inhibition of Btk enzymatic activity [23]. These two anticancer drugs, Blinatumomab and Ibrutinib-Rituximab, have yielded high success rates of progression-free survival and overall survival [23,25-27]. In detail, 2-year disease-free survival was found to be 39.0% for patients given intensive chemotherapy with each drug, whereas it was 54.4% for patients given the standard drug treatments [25]. In addition, 2-year overall survival was relatively worse (58.4%) in patients treated with standard chemotherapy treatments compared to those with these two drugs (71.3%) [24,25,28].

Radiotherapy has also been used for retreatment of leukemia in patients who have experienced relapse after remission and has been found to be more effective in the long term in preventing further relapses and increasing overall survival rates [29]. Radiotherapy uses high doses of ionizing radiation to target and kill or damage cancer cells while minimizing damage to surrounding healthy tissues [30]. The high-energy particles from the ionizing radiation penetrate the body and collide with atoms and molecules, creating charged particles and free radicals that can damage the cellular DNA [30]. Cancer cells are more susceptible than healthy cells to the lethal effects of radiation owing to their uncontrolled growth and reduced ability to repair DNA damage that disrupts their ability to divide and grow. Radiotherapy, when used in conjunction with other cancer treatments, such as chemotherapy or immunotherapy, yields better patient outcomes [29]. For example, patients treated with cranial radiation followed by

maintenance chemotherapy experienced a 78% response rate to the treatment and had a 4-year survival rate of 77.7%, compared with the survival rate of 11.3% of patients who were treated with chemotherapy alone [29].

For most pediatric leukemias, the most effective form of treatment is allogenic stem cell therapy, which yields a higher remission rate than chemotherapies, radiotherapy, and other treatments [31,32]. Allogenic stem cell therapy involves the transplantation of stem cells from a genetically different, healthy donor to a recipient who has a medical condition, such as a hematologic disorder like leukemia [33,34]. It offers the advantage of providing a new source of healthy stem cells to replace damaged or diseased cells, and it can significantly improve the recipient's condition [21,33,35]. However, shortly after this treatment, a significant portion of the patients experienced relapse or rejection, ultimately leading to death [31-33].

Of note, during the last 10 years, some immunotherapies have been discovered that have been of special interest, being reportedly more effective than most traditional chemotherapies, radiotherapy, and stem cell treatments [21,36-39]. Immunotherapies treat cancer by either activating or suppressing the immune system. One such agent, tisagenlecleucel, a chimeric antigen receptor (CAR) T-cell therapy, has been approved to treat relapsed pediatric leukemia (**Figure 1**) [39,40]. This highly specialized CAR T-cell therapy involves genetically modifying a patient's own T cells to recognize and attack the antigen found on the surface of



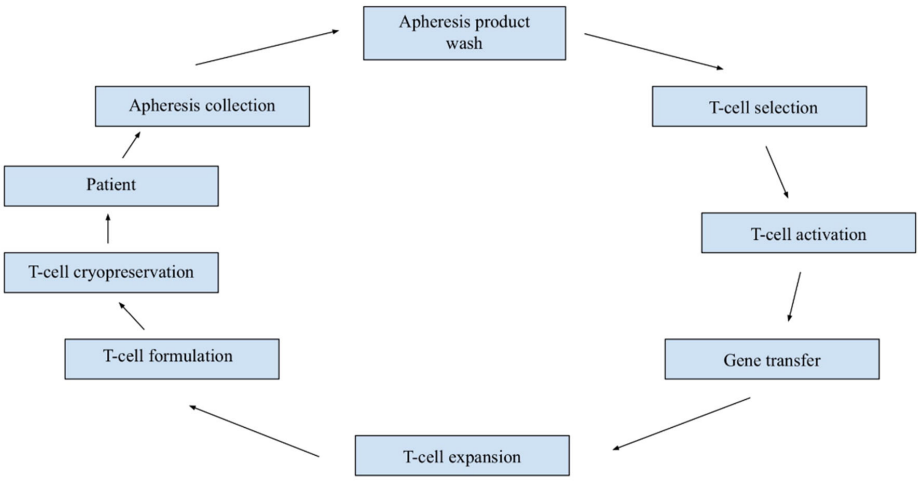


Figure 1: An overview of the CAR T cell creation and treatment process.

specific cancer cells. In manufacturing the CAR T cells, a protein is added to the T cells' surface to help them achieve this focus. The CAR protein is composed of three distinct proteins: one for recognition of the antigen on the cancer cell and two for T-cell activation when the first protein binds to the cancer cell antigen [41]. These activated T cells then circulate, looking for cells that carry the antigen programmed into the CAR protein. When they come into contact with the cancer cells' antigen, they multiply and activate other immune cells to fight off the malignant cells. These signaling proteins, or cytokines, along with activated T cells, induce notable inflammation, ultimately resulting in the death of the cancer cells [41]. If all the cancer cells die, the cancer is in remission. CAR T-cell treatment has achieved survival rates of more than 50% for both initial and tertiary remission 5–10 years after treatment among children and teens [37,42]. A drawback to CAR-T therapy, however, is its frequent association with various end-organ toxicities, such as profound neurotoxicity and cytokine release syndrome, which potentially restrict its effectiveness, particularly in patients with diminished performance status or comorbidities.

Other, more recently developed novel therapeutic modalities, including bispecific T-cell engagers (BiTEs) and bispecific antibodies (BiAbs), have now surfaced as valuable approaches in addressing advanced hematologic malignancies [43]. BiTEs and BiAbs redirect T cells to attack tumors and facilitate T cell–mediated cell death [43]. Blinatumomab, mentioned earlier, is a CD19/CD3 BiAb that was the pioneering BiTE molecule. It demonstrated remarkable proof of concept and has been approved by the U.S. Food and Drug Administration for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia [43,44]. BiAbs and BiTEs provide T cell–redirecting capabilities akin to those of CAR-T cell therapy, but in the form of a ready-to-use therapy, circumventing the logistical and time-related challenges inherent in the creation and delivery of CAR T cells [44,45]. Additionally, BiAbs and BiTEs seem to exhibit a more favorable safety profile than CAR T-cell therapy, with lower incidences of cytokine release syndrome and neurotoxicity [44-46].

Overall, the effectiveness of these treatments to prevent tertiary leukemia hinges on a multidrug protocol comprising three stages (induction, consolidation, and maintenance), wherein therapy or prophylaxis targeting the central nervous system is administered across several sessions. Among overall treatments we examined in this review, CAR T-cell therapy is considered a promising treatment, having high success rates after patient relapse.

Although we found limited information in our literature search specific to tertiary prevention of leukemia and its relapse, we understand the potential bias of the search strategy we used in terms of the possibility of missing relevant articles with the limited data sources we searched. However, continuing research into more innovative treatments is needed to prolong the lifespan for all patients with leukemia. Further, we call for more research on immunotherapies to explore their effectiveness in tertiary and quaternary prevention of leukemias in populations of even more diverse age groups, including the elderly.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Davis AS, Viera AJ, Mead MD. Leukemia: an overview for primary care. Am Fam Physician. 2014 May 1;89(9):731-8.
2. Lim JY, Bhatia S, Robison LL, Yang JJ. Genomics of racial and ethnic disparities in childhood acute lymphoblastic leukemia. Cancer. 2014 Apr 1;120(7):955-62
3. Greaves M. Author Correction: A causal mechanism for childhood acute lymphoblastic leukaemia. Nat Rev Cancer. 2018 Aug;18(8):526.
4. Gu KJ, Li G. An Overview of Cancer Prevention: Chemoprevention and Immunoprevention. J Cancer Prev. 2020 Sep 30;25(3):127-35.
5. Krstic MN, Mijac DD, Popovic DD, Pavlovic Markovic A, Milosavljević T. General Aspects of Primary Cancer Prevention. Dig Dis. 2019;37(5):406-15.
6. Whitehead TP, Metayer C, Wiemels JL, Singer AW, Miller MD. Childhood Leukemia and Primary Prevention. Curr Probl Pediatr Adolesc Health Care. 2016 Oct;46(10):317-52.
7. Eddy DM. Secondary prevention of cancer: an overview. Bull World Health Organ. 1986;64(3):421-9.
8. Jacobsen PB, Andrykowski MA. Tertiary prevention in cancer care: understanding and addressing the psychological dimensions of cancer during the active treatment period. Am Psychol. 2015 Feb-Mar;70(2):134-45.
9. Tesser CD. Why is quaternary prevention important in prevention? Rev Saude Publica. 2017 Dec 4;51:116.
10. Huang J, Chan SC, Ngai CH, Lok V, Zhang L, Lucero-Prisno DE 3rd, et al. Disease Burden, Risk Factors, and Trends of Leukaemia: A Global Analysis. Front Oncol. 2022 Jul 22;12:904292.
11. Leukemia Awareness and Prevention | Leukemia | UT Southwestern Medical Center. http://utswmed.org/conditions-treatments/leukemia/leukemia-awareness-and-prevention/. Accessed 23 Dec 2023.
12. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020 Oct 13;4(19):4693-738.
13. When Cancer Comes Back. In: Clevel. Clin. https://my.clevelandclinic.org/health/articles/24872-cancer-recurrence. Accessed 23 Dec 2023.

14. When Cancer is in Remission. In: Clevel. Clin. https://my.clevelandclinic.org/health/articles/24673-cancer-remission. Accessed 23 Dec 2023.

15. Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009 Jun 25;360(26):2730-41.

16. Gilliland DG, Jordan CT, Felix CA. The molecular basis of leukemia. Hematology Am Soc Hematol Educ Program. 2004:80-97.

17. Chemotherapy to Treat Cancer - NCI. 2015. https://www.cancer.gov/about-cancer/treatment/types/chemotherapy. Accessed 23 Dec 2023

18. Saleem T, Kasi A. Daunorubicin. 2023 Aug 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.

19. Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, McLeod H, Klein TE, et al. Doxorubicin pathways: pharmacodynamics and adverse effects. Pharmacogenet Genomics. 2011 Jul;21(7):440-6.

20. Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. Leuk Lymphoma. 2015;56(8):2273-80.

21. Soiffer RJ, Kim HT, McGuirk J, Horwitz ME, Johnston L, Patnaik MM, et al. Prospective, Randomized, Double-Blind, Phase III Clinical Trial of Anti-T-Lymphocyte Globulin to Assess Impact on Chronic Graft-Versus-Host Disease-Free Survival in Patients Undergoing HLA-Matched Unrelated Myeloablative Hematopoietic Cell Transplantation. J Clin Oncol. 2017 Dec 20;35(36):4003-11.

22. Mocquot P, Mossazadeh Y, Lapierre L, Pineau F, Despas F. The pharmacology of blinatumomab: state of the art on pharmacodynamics, pharmacokinetics, adverse drug reactions and evaluation in clinical trials. J Clin Pharm Ther. 2022 Sep;47(9):1337-51.

23. Shanafelt TD, Wang XV, Kay NE, Hanson CA, O'Brien S, Barrientos J, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med. 2019 Aug 1;381(5):432-43.

24. Kater AP, Wu JQ, Kipps T, Eichhorst B, Hillmen P, D'Rozario J, et al. Venetoclax Plus Rituximab in Relapsed Chronic Lymphocytic Leukemia: 4-Year Results and Evaluation of Impact of Genomic Complexity and Gene Mutations From the MURANO Phase III Study. J Clin Oncol. 2020 Dec 1;38(34):4042-54.

25. Brown PA, Ji L, Xu X, Devidas M, Hogan LE, Borowitz MJ, et al. Effect of Postreinduction Therapy Consolidation With Blinatumomab vs Chemotherapy on Disease-Free Survival in Children, Adolescents, and Young Adults With First Relapse of B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA. 2021 Mar 2;325(9):833-42.

26. Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019 Dec;94(12):1353-63.

27. van Oers M, Smolej L, Petrini M, Offner F, Grosicki S, Levin MD, et al. Ofatumumab maintenance prolongs progression-free survival in relapsed chronic lymphocytic leukemia: final analysis of the PROLONG study. Blood Cancer J. 2019 Dec 4;9(12):98.

28. Avet-Loiseau H, Ludwig H, Landgren O, Paiva B, Morris C, Yang H, et al. Minimal Residual Disease Status as a Surrogate Endpoint for Progression-free Survival in Newly Diagnosed Multiple Myeloma Studies: A Meta-analysis. Clin Lymphoma Myeloma Leuk. 2020 Jan;20(1):e30-7.

29. Strosberg J, Leeuwenkamp O, Siddiqui MK. Peptide receptor radiotherapy re-treatment in patients with progressive neuroendocrine tumors: A systematic review and meta-analysis. Cancer Treat Rev. 2021 Feb;93:102141.

30. Radiation Therapy for Cancer - NCI. 2015. https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy. Accessed 23 Dec 2023

31. Braga Lemos M, Rodrigues SR, Schroeder T, Kulasekararaj AG, Matos JE, et al. Association between red blood cell transfusion dependence and burden in patients with myelodysplastic syndromes: A systematic literature review and meta-analysis. Eur J Haematol. 2021 Jul;107(1):3-23.

32. Khimani F, Dutta M, Faramand R, Nishihori T, Perez AP, Dean E, et al. Impact of Total Body Irradiation-Based Myeloablative Conditioning Regimens in Patients with Acute Lymphoblastic Leukemia Undergoing Allogeneic Hematopoietic Stem Cell Transplantation: Systematic Review and Meta-Analysis. Transplant Cell Ther. 2021 Jul;27(7):620.e1-620.e9.

33. Giralt S, Bishop MR. Principles and overview of allogeneic hematopoietic stem cell transplantation. Cancer Treat Res. 2009;144:1-21.

34. Wanquet A, Bramanti S, Harbi S, Fürst S, Legrand F, Faucher C, et al. Killer Cell Immunoglobulin-Like Receptor-Ligand Mismatch in Donor versus Recipient Direction Provides Better Graft-versus-Tumor Effect in Patients with Hematologic Malignancies Undergoing Allogeneic T Cell-Replete Haploidentical Transplantation Followed by Post-Transplant Cyclophosphamide. Biol Blood Marrow Transplant. 2018 Mar;24(3):549-54.

35. Samimi A, Ghanavat M, Shahrabi S, Azizidoost S, Saki N. Role of bone marrow adipocytes in leukemia and chemotherapy challenges. Cell Mol Life Sci. 2019 Jul;76(13):2489-97.

36. Lato MW, Przysucha A, Grosman S, Zawitkowska J, Lejman M. The New Therapeutic Strategies in Pediatric T-Cell Acute Lymphoblastic Leukemia. Int J Mol Sci. 2021 Apr 26;22(9):4502.

37. Iqbal M, Reljic T, Klocksieben F, Sher T, Ayala E, Murthy H, et al. Efficacy of Allogeneic Hematopoietic Cell Transplantation in Human T Cell Lymphotropic Virus Type 1-Associated Adult T Cell Leukemia/Lymphoma: Results of a Systematic Review/Meta-Analysis. Biol Blood Marrow Transplant. 2019 Aug;25(8):1695-1700.

38. Saglio G, Gale RP. Prospects for achieving treatment-free remission in chronic myeloid leukaemia. Br J Haematol. 2020 Aug;190(3):318-27.

39. Pasquini MC, Hu ZH, Curran K, Laetsch T, Locke F, Rouce R, et al. Real-world evidence of tisagenlecleucel for pediatric acute

lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Adv. 2020 Nov 10;4(21):5414-24.

40. Ma S, Li X, Wang X, Cheng L, Li Z, Zhang C, et al. Current Progress in CAR-T Cell Therapy for Solid Tumors. Int J Biol Sci. 2019 Sep 7;15(12):2548-60.

41. CAR T Cells: Engineering Immune Cells to Treat Cancer - NCI. 2013. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells. Accessed 23 Dec 2023.

42. Aamir S, Anwar MY, Khalid F, Khan SI, Ali MA, Khattak ZE. Systematic Review and Meta-analysis of CD19-Specific CAR-T Cell Therapy in Relapsed/Refractory Acute Lymphoblastic Leukemia in the Pediatric and Young Adult Population: Safety and Efficacy Outcomes. Clin Lymphoma Myeloma Leuk. 2021 Apr;21(4):e334-e347.

43. Goebeler ME, Bargou RC. T cell-engaging therapies - BiTEs and beyond. Nat Rev Clin Oncol. 2020 Jul;17(7):418-434.

44. Goebeler ME, Bargou R. Blinatumomab: a CD19/CD3 bispecific T cell engager (BiTE) with unique anti-tumor efficacy. Leuk Lymphoma. 2016 May;57(5):1021-32.

45. Ruella M, Gill S. How to train your T cell: genetically engineered chimeric antigen receptor T cells versus bispecific T-cell engagers to target CD19 in B acute lymphoblastic leukemia. Expert Opin Biol Ther. 2015 Jun;15(6):761-6.

46. Einsele H, Borghaei H, Orlowski RZ, Subklewe M, Roboz GJ, Zugmaier G, Kufer P, Iskander K, Kantarjian HM. The BiTE (bispecific T-cell engager) platform: Development and future potential of a targeted immuno-oncology therapy across tumor types. Cancer. 2020 Jul 15;126(14):3192-3201.