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PAEDIATRIC LYMPHOMA: A COMPREHENSIVE REVIEW OF TREATMENT OPTIONS

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ABSTRACT

Pediatric lymphoma is a diverse group of malignancies that account for approximately 10% of childhood cancers. It is a highly treatable malignancy, with cure rates including 80% for many subtypes. This review offers a thorough overview of the current classification system, staging criteria, and treatment approaches for pediatric lymphoma. Hodgkin's and non-Hodgkin's lymphoma are the two main categories of lymphoma. A distinctive type of lymphoma known as Hodgkin lymphoma is distinguished by the presence of Reed-Sternberg cells and the histopathologic characteristics of Hodgkin lymphoma cannot be distinguished from non-Hodgkin lymphoma, a heterogenous group of lymphoid neoplasms that can arise from mature or immature (lymphoblastic) natural killer cells, T-cells, or B-cells. This review encompasses the revised International Paediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS), the Ann Arbor staging system, the St. Jude system, and the World Health Organization (WHO) classification system. It also covers treatment options such as radiation therapy, chemotherapy, immunotherapy, stem cell transplantation, and new agents like CAR-T cell therapy.

KEYWORD:- Hodgkin lymphoma, non-Hodgkin lymphoma, world health organization (WHO), CAR-T cell therapy, Reed-Sternberg cells, natural killer cells, T-cells, B-cells.

INTRODUCTION

Lymphoma is the third most frequent cancer in children and is a neoplastic condition that results from the malignant alteration of lymphoid cells.[1] The prevalence of lymphoma in childhood cancers is approximately 10%.[2] The term "lymphoma" describes the malignant proliferation of lymphoid cells, typically found in or originating from lymphoid tissues (Such as the spleen, thymus, or lymph nodes).[6] The majority of individuals with lymphoma have a disease-free survival rate of over 85%, making it one of the most treatable pediatric diseases nowadays. Lymphomas are a broad category of immune system-related malignancies. Based on genomic traits and histological findings, they are traditionally classified into two main groups: Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL).[1] NHL is more common in children under the age of 15, but Hodgkin's disease predominates in patients up to the age of 18. NHL incidence rises gradually throughout life, whereas Hodgkin's disease has a bimodal age distribution with peaks in early and late adulthood.[4] NHL accounts for the majority of lymphoma cases, with recent statistics indicating that over 500,000 NHL occur annually around the world.[3]

Advances in lymphoma biology, together with improved staging, treatment, and response evaluations, have paved the path for risk- and response-specific medicines with improved outcomes and fewer long-term side effects.[1] Paediatric lymphoma management is difficult and necessitates an individualized strategy based on the specific type, stage, and individual patient characteristics. Current therapy for treating children with Hodgkin lymphoma and various histological subtypes of non-Hodgkin lymphoma have resulted in overall survival rates that exceed 90% in many cases.[5]

Hodgkin lymphoma

Thomas Hodgkin imparted the first description of a lymphoma in 1832, and it was named after him as Hodgkin's lymphoma. Hodgkin's lymphoma, often known as Hodgkin's disease (HD), causes progressive lymph node growth. It is thought to have a unicentric origin and spreads in a predictable pattern to contiguous lymph nodes.[6] Hodgkin lymphoma (HL) is a distinct monoclonal lymphoid cancer distinguished by the presence of typical bi/multinucleated Reed-Sternberg cells and their variations, mononucleated Hodgkin cells, also known as Hodgkin Reed-Sternberg cells (HRS). The

majority of HRS cells express CD15 and CD30 (85% and 100%, respectively, in HL patients.[8]

Hodgkin's disease was the first malignancy to be cured by radiation therapy alone or in combination with other chemotherapeutic medicines, even before the biology of the illness was easier to comprehend. Since then, the cure rate for Hodgkin's disease in children and adolescents has progressively improved, mainly in large part to the use of combination radiation and multi-agent chemotherapy.[6] Childhood HL accounts for 6% of all malignancies and has an incidence rate of 12 cases/million per year in the 0-14 age group, with a male predominance.[7]

The WHO amended and adopted the Revised European-American Lymphoma (REAL) classification, which is the most recent and currently accepted classification:

1. Classic hodgkin's lymphoma

Classic nodular sclerosis: presence of fibrous bands that generate a nodular pattern in lacunar-type Hodgkin-Reed Sternberg (HRS) cells, in which the cytoplasm retracts in formalin-fixed specimens, forming a lacuna around the nucleus. This is the most prevalent kind across all age groups (77% of teenagers and 72% of adults), however it only affects 44% of younger children.

Classic mixed cellularity: Although fibrous bands are absent in this type, interstitial fibrosis may be present. HRS cells are either mononuclear or have a characteristic appearance. In the cellular background, lymphocytes could be the predominant cell type. Compared to teenagers (11%) and adults (17%), young children (33%) are more likely to have this subtype.

Classic lymphocyte rich: This type is quite uncommon and features HRS cells of the classic or lacunar types with infrequent or nonexistent eosinophils on a cellular background.

Classic lymphocyte depleted: Numerous HRS cells have sarcomatous variations and a hypocellular background as a result of necrosis and fibrosis. It is likewise very uncommon.

2. Nodular lymphocyte predominance (NLP)

Fibrosis is uncommon in this form, which may be nodular. Popcorn cells, also known as lymphocytic and histiocytic (L&H) cells, are the different types of HRS cells. The vesicular, multilobed nuclei have tiny nucleoli. There is no longer the distinctive halo of the traditional H-RS cell. Unlike the cellular background in conventional HD, which is dominated by T cells, the background is composed of histiocytes and lymphocytes with a B-cell predominance.[6]

Classic and nodular lymphocyte predominance are the two main subtypes of Hodgkin lymphoma in children. Residual non-viable tissue is frequently observed following therapy in Hodgkin lymphoma because the tumor has a high amount of collagen and fibrous stroma and only a limited number of malignant cells. Hodgkin lymphoma primarily affects teenagers (15–19 years old) and is more common in developed nations. Since pediatric Hodgkin lymphoma has a 5-year survival rate of over 98% and cure rates of 90% to 95%, it is typically quite susceptible to chemotherapy and radiation.[1]

Staging

The ann arbor staging system with cotswold modifications, which takes into account both clinical and imaging evidence, is the most often used staging system for pediatric Hodgkin lymphoma. According to the Ann Arbor approach, nodal stations are separated into anatomic sites (such as the cervical, axillary, and mediastinal) and the stage is determined by the number of implicated sites. In stage 1, the disease only affects one nodal site or region (such as the spleen, thymus, or Waldeyer ring, which are all considered nodal tissue). Stage 2 disease involves two or more sites on one side of the diaphragm, while Stage 3 disease includes two or more sites on both sides of the diaphragm. Stage 4 disease includes extra-nodal involvement or disease that is widely dispersed. Other modifiers are: A (no specific constitutional symptoms), B (constitutional "B" symptoms), E (extra-nodal involvement), S (splenic involvement), and X (bulky nodal mass).[1]

Treatment

Hodgkin lymphoma (HL) is one of the most treatable malignancies in both children and adults, with long-term survival rates already above 90% following treatment with chemotherapy alone or in conjunction with radiation therapy (RT).[9]

Conventional-dose salvage treatment and radiotherapy were used to treat patients in the low-risk category. The standard-risk group underwent autologous stem cell transplantation after receiving conventional-dose salvage chemotherapy and consolidation with high-dose chemotherapy. Individuals in the high-risk group were potential candidates for experimental treatments or autologous or allogeneic transplantation.[17]

Modern chemotherapy combined with involved field radiation therapy (IFRT) is the first-line treatment for HL in children.[19]

Consolidative radiation therapy (RT) and chemotherapy are the first steps in the treatment of pediatric Hodgkin lymphoma. Without sacrificing results, the goal is to increase cure rates while eliminating subsequent adverse effects with risk- and response-adapted medicines.[20]

Most pediatric patients respond best to combined-modality therapy, which includes chemotherapy and radiation. The choice of a treatment plan is crucial when treating children and adolescents with Hodgkin lymphoma because the majority of these patients respond well to treatment, especially when taking into account

the potential late toxicities of cancer-directed therapy. There are significant differences in late toxicities depending on the type of treatment.

The majority of contemporary pediatric treatment approaches use response-adjusted combined-modality regimens or risk-adapted chemotherapy alone to minimize late effects of therapy while preserving high cure rates.[21]

Chemotherapeutic agents

Hodgkin lymphoma is treated with a variety of chemotherapeutic drugs in different combinations. Depending on the disease stage, the combinations change. To prevent the large cumulative dosages of bleomycin, anthracyclines, and alkylating drugs used in chemotherapy-only protocols, combined-modality therapy is recommended.

Children's multiagent chemotherapy regimens have been created to prevent or lessen the risk of cardio pulmonary toxicities, leukemia, and sterility.

The following are the most common treatment plans for Hodgkin lymphoma in children:

European regimens

OPPA: Vincristine (Oncovin), Procarbazine, Prednisone and Doxorubicin (Adriamycin)
OEPA: Vincristine (Oncovin), Etoposide, Prednisone and Doxorubicin (Adriamycin)
COPP: Cyclophosphamide, Vincristine, Procarbazine and Prednisone
COPDAC: Cyclophosphamide, Vincristine, Prednisone and Dacarbazine
VBVP: Vinblastine, Bleomycin, Etoposide and Prednisone

American regimens (Children's Oncology Group)

ABVE: Doxorubicin, bleomycin, vincristine, and etoposide
ABVE-PC: Doxorubicin (Adriamycin), Bleomycin, Vincristine, Etoposide, Prednisone and Cyclophosphamide
BEACOPPesc: Bleomycin, Etoposide, Doxorubicin (Adriamycin), Cyclophosphamide, Vincristine, Procarbazine and prednisone
COPP/ABV: Cyclophosphamide, Vincristine, Procarbazine, Prednisone, Doxorubicin (Adriamycin), Bleomycin and vinblastine
VAMP/COP: Vincristine, Doxorubicin (Adriamycin), Methotrexate and prednisone alternating with cyclophosphamide, vincristine, and prednisone
Stanford V: Doxorubicin (Adriamycin), Vinblastine, Mechlorethamine, Vincristine, Bleomycin, Etoposide and prednisone.[22][23]

Immunotherapy

Immunotherapy, also known as biologic therapy, is intended to strengthen the body's natural defences against cancer. It uses components produced by the body or in a laboratory to improve, target, or restore immune system function.

The Food and Drug Administration (FDA) has approved nivolumab (Opdivo) and pembrolizumab (Keytruda) as immunotherapies for the treatment of recurrent HL. These can be used to treat HL that has progressed following several previous treatments, including auto transplantation and post-transplant brentuximab vedotin.

Radiation therapy

After chemotherapy, radiation is utilized as an adjuvant treatment. To eradicate cancer cells, high-energy x-rays or other particles are used in radiotherapy. External-beam radiation treatment, which involves administering radiation from an apparatus outside the body, is typically used as a radiation treatment for HL. Schedules for radiation therapy usually include a special range of treatments administered over a predetermined amount of time. Radiation that is low dosage, involved field, extended field, risk-adapted, or response-based is used to minimize complications. To minimize adverse effects, radiation is often exclusively applied to the afflicted lymph node areas. The acute side effects of radiation therapy vary depending on the region of the body being treated. Even while the likelihood of long-term side effects has decreased as treatment has advanced, radiation therapy can still result in long-term adverse effects, sometimes known as late effects.

Bone marrow transplantation/stem cell transplantation

A bone marrow transplant is a scientific procedure whereby specialized cells are used to replace bone marrow that has been harmed or impacted by malignancy. Hematopoietic stem cells are cells that have the ability to differentiate into healthy bone marrow. Hematopoietic stem cells are blood-forming cells that can be found in both the circulation and bone marrow. This procedure is now more frequently referred to as a stem cell transplant than a bone marrow transplant. This is because stem cells not from the actual bone marrow tissue are being transplanted; instead, stem cells are often extracted from the blood. As a first-line therapy for HL, this is not advised. This is frequently used for persons who have lymphoma that remains after chemotherapy or who have a cancer recurrence.[19]

Table no. 1: Chemotherapy regimens for paediatric Hodgkin lymphoma.[26,27,28,29,30]

Regimen	Drugs	Dose(mg/m^2)	Days	Frequency	Route
ABVD	Doxorubicin	25	1, 15		IV
	Bleomycin Vinblastine	10	1, 15	28 days	IV

	Dacarbazine	6 375	1, 15 1, 15		IV IV
Stanford V	Doxorubicin Vinblastine Mechlorethamine Vincristine Bleomycin Etoposide Prednisone	25 6 6 1.4 5 60 40	1, 15, 29, 43, 57, 71 1, 15, 29, 43, 57, 71 1, 29, 57 8, 22, 36, 50, 64, 78 8, 22, 36, 50, 64, 78 15, 43, 71 qod for 12 weeks	28 days	IV IV IV IV IV IV Oral
BEACOPP (basic)	Bleomycin Etoposide Doxorubicin Cyclophosphamide Vincristine Procarbazine Prednisone	10 100 25 650 1.4 100 40	8 1-3 1 1 8 1-7 1-14	21 days	IV IV IV IV IV Oral Oral
BEACOPP (escalated	Bleomycin Etoposide Doxorubicin Cyclophosphamide Vincristine Procarbazine Prednisone	10 200 35 1250 1.4 100 40	8 1-3 1 1 8 1-7 1-14	21 days	IV IV IV IV IV Oral Oral
COPDAC	Cyclophosphamide Vincristine (Oncovin) Prednisone Dacarbazine	600 1.4 40 250	1,8 1,8 1-15 1-3	21-28 days	IV IV Oral IV
OEPA	Vincristine (oncovin) Etoposide Prednisone Doxorubicin (Adriamycin)	1.5 125 60 40	1,5,8 3-6 1-15 1,15	21-28 days	IV IV Oral IV
ABVE-PC	Doxorubicin (Adriamycin) Bleomycin Vincristine (oncovin) Etoposide Prednisone Cyclophosphamide	30 10 units/m^2 1.4(maximum dose, 2.8) 75 40 800	0,1 0,7 0,7 0-4 0-9 0	21-28 days	IV IV IV IV Oral IV

Treatment for favourable-risk paediatric Hodgkin lymphoma

- For early or favourable disease (stage IA or IIA with <3 nodal sites, and some IIIA without bulky disease) the standard treatment consists of 2-4 chemotherapy cycles of ABVE, OEPA, or VAMP plus either 6 chemotherapy cycles of COPP alternating with ABVD and no irradiation, or low-dose, involved-field radiation of 15-30 Gy. In terms of cumulative chemotherapy doses and survival, the adult regimen ABVD is comparable for cycles 2-4. Other regimens expose patients to needless dosages of chemotherapy; however, they are safe, practical, and effective. Treatment of paediatric Hodgkin lymphoma that is progressed or unfavourable.
- For intermediate-risk diseases (stage IIA bulky disease with extension or three nodal locations, stage IIB, stage III, and stage IV) The typical treatment consists of 3-5 cycles of ABVE-PC with 21 Gy of involved-field radiation, depending on the patient's reaction to induction treatment. The treatment plan reduces each patient's overall chemotherapy exposure while providing efficient chemotherapy in a dose-dense manner.

Treatment for advanced or unfavourable disease (stages IIB, IIIB, or IV)

One of the three approaches specified below is applied:

- The OEPA regimen lowers gonado-toxicity by substituting etoposide for procarbazine. Additionally, it is well tolerated and efficacious in the pediatric population when combined with COPP or COPDAC.

- The BEACOPP regimen is quite effective, but the cumulative chemotherapeutic dosages are problematic. Patients with stage IVB illness benefit from this regimen the most.
- Reducing the use of radiation therapy for patients in this group has decreased their event-free survival.[24]

Retrieval therapies for relapsed hodgkin lymphoma

Autologous stem cell transplantation dramatically extends disease-free life in individuals with recurrent or nonresponsive illness. With stem cell rescue, a variety of medication combinations have been employed.

The most popular reinduction therapy for children with Hodgkin lymphoma in the US is Ifosfamide, carboplatin, and etoposide (ICE). Even though ICE can bring patients into second remission, it is not a viable choice because it is linked to myelosuppression and a higher risk of secondary malignant neoplasms that are related to treatment and are caused by alkylating drugs and epipodophyllotoxins.

Other retrieval regimens have been demonstrated to be safe and successful as a reinduction regimen for relapsed pediatric Hodgkin lymphoma, including the combination of ifosfamide and vinorelbine (IV) or gemcitabine and vinorelbine (GV). They have the advantage of removing the usage of etoposide, hence lowering the risk of treatment-related secondary myelodysplasia and acute myelocytic leukemia.[25]

Table no. 2: Novel target drugs.[18]

Drug	Class	Function
Brentuximab vedotin (Bv, SGN35)	Anti-CD30 drug-conjugate antibody	It blocks the cell cycle and triggers apoptosis of HRS. It combined with chemotherapy for stage III-IV disease
Nivolumab Pembrolizumab	anti-programmed cell death protein 1 (PD-1) inhibitor	Inhibitor of PD-1/PD-L1 immune checkpoint
Sintilimab, camrelizumab, tislelisumab	PD-1 inhibitor	Inhibitor of PD-1/PD-L1 immune checkpoint
Ipilumumab	CTLA-4	Inhibitor of CTLA-4/CD80 and CD86 immune checkpoint
Trabectedin	CD30/CD37	A bispecific antibody targeting CD30 and CD37, both members of the tumor necrosis factor receptor family
Vorinostat	Histone deacetylase (HDAC) inhibitors.	Histones regulate gene expression and chromosome packaging during cell division
Decitabine	DNA methyltransferase (DNMT) inhibitors.	In particular, EBV infection is associated with an altered expression of specific DNMTs
Ruxolitinib, Fedratinib Itacitinib	JAK inhibitors	Inhibitors of Janus kinases (JAK), selective for JAK1 and JAK2
Selinexor	XPO1 inhibitor	Selective inhibitor of nuclear exportin 1 (XPO1) protein simultaneously inhibiting several active tumorigenic processes and also synergizing with other targeted drugs and chemotherapy
Everolimus Idelalisib	mTOR inhibitor	Everolimus developed as an analog of rapamycin, an inhibitor of the serine protein kinase mTOR. Idelalisib, a PI3K inhibitor, reduces activation of the PI3K/Akt/mTOR pathway.
Car-T	T- cell based therapy	Chimeric antigen receptor modified T (Car-T) cell-based therapy gives T lymphocytes the ability to combine both antigen recognition and T cell activation functions into a single receptor

Nonhodgkin lymphoma

Non-Hodgkin lymphoma is a diverse category of lymphoid neoplasms that lack the histopathologic hallmarks of Hodgkin lymphoma and can arise from mature or immature B-cells, T-cells, or natural killer cells (lymphoblastic). Non-Hodgkin's lymphomas (NHL) in children are distinguished by predominant extranodal disease and rapid tumor growth and dissemination,

particularly into the bone marrow and central nervous system (CNS).[10] Despite Hodgkin lymphoma tumors, which contain only a few malignant cells, most paediatric non-Hodgkin lymphoma tumors contain 85%-99% highly proliferating malignant cells.

Non-Hodgkin lymphoma is more common in developing countries, affects younger children (under the age of nine), and is typically more aggressive than Hodgkin lymphoma. Cure rates vary by subtype and stage, but are typically between 70% and 90% with rigorous treatment.[1]

Non-Hodgkin lymphoma is more common in developing countries, affects younger children (under the age of nine), and is typically more aggressive than Hodgkin lymphoma. Cure rates vary by subtype and stage, but are typically between 70% and 90% with rigorous treatment.[1] Lymphoma survivors are prone to acquire secondary malignancies as a result of previous radiation therapy, such as thyroid cancer, sarcoma, and breast cancer. Survivors are also more prone to develop chemotherapy-related complications, such as cardiovascular disease from cardiotoxic anthracyclines and impaired fertility from gonadotoxic alkylating drugs. Over the last few decades, many studies have focused on risk assessment and treatment-response adaptive therapies, with the goal of reducing radiation and chemotherapy overtreatment and hence adverse effects.[1]

Staging

Non-Hodgkin lymphoma is staged using the St. Jude classification by Murphy or the revised International Pediatric Non-Hodgkin Lymphoma Staging System.

The number, location, and degree of extra-nodal involvement of the lymph nodes are the basis for the St. Jude system's four-stage classification of non-Hodgkin lymphoma. Stage 1 is characterized by a single extra-nodal tumor or lymph node that is not located in the abdomen or mediastinum and does not entail any regional involvement. Stage 2 is characterized by a primary resectable gastrointestinal tumor (Usually ileocecal) with or without mesenteric nodal involvement, two or more disease sites (With or without regional involvement) on one side of the diaphragm, or a single extra-nodal tumor with regional involvement. Stage 3 includes involvement on both sides of the diaphragm, without CNS or bone marrow involvement, and primary intrathoracic tumors affecting the mediastinum, pleura, thymus, intra-abdominal disease, or paraspinal/epidural tumors. Stage 4 is characterized by disease in the central nervous system or bone marrow, with or without involvement of other locations.[1]

The revised International Paediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS) was introduced in 2015 and takes into consideration additional sites of extra-nodal illness, including mucosal, cutaneous, cortical bone, ovarian, and renal involvement. Stage 1 contains a single nodal or extra-nodal site, and also determines whether there is skin or cortical bone involved. Regardless of position with respect to the diaphragm, stage 2 consists a single extra-nodal tumor with regional involvement, two or more nodal areas on the same side of the diaphragm, and a resectable GI primary tumor with associated mesenteric nodes only, without multiorgan involvement (e.g., direct invasion of adjacent structures or peritoneal disease). Stage 3 comprises intrathoracic (mediastinal, hilar, pulmonary, pleural, or thymic) and spinal/epidural tumors, the designation of skin, cortical bone, ovarian or renal involvement, two or more nodal sites above and below the diaphragm, two or more extra-nodal sites, regardless of position with respect to the diaphragm, and a single bone lesion combined with extra-nodal or non-regional nodal involvement. In stage four, any of the earlier locations with bone marrow disease, CNS disease, or both (stage 4 combined) are included.[1]

Table no. 3: Types of Non-Hodgkin Lymphoma.
The table categorizes various non-Hodgkin's lymphoma (NHL) types.[11,12]

WHO classification (Sub type)	Type of NHL	Immunophenotype	Clinical presentation
Burkitt lymphoma (BL)	Mature B-cell NHL	Mature B-cell	Intra-abdominal (sporadic), head and neck (non-jaw, sporadic), jaw (endemic), bone marrow, CNS
Burkitt-like lymphoma with 11q aberration (provisional) (BLL)	Mature B-cell NHL	Mature B-cell	Nodal, 11q alteration, no MYC rearrangement
Large B-cell lymphoma with IRF4 rearrangement (LBCL)	Mature B-cell NHL	Mature B-cell	Nodal (typically head and neck), Cryptic IRF4 rearrangement with immunoglobulin heavy (IGH) locus
Diffuse large B-cell lymphoma (DLBCL)	Mature B-cell NHL	Mature B-cell	Nodal, abdominal, bone, primary CNS (when associated with immunodeficiency), mediastinal, No consistent cytogenetic abnormality identified

Primary mediastinal (thymic) large B-cell lymphoma (PMBCL)	Mature B-cell NHL	Mature B-cell, often CD30+	Mediastinal, but may also have other nodal or extra-nodal disease (i.e., abdominal, often kidney
ALK-positive large B-cell lymphoma	anaplastic large cell lymphoma	CD20, CD30, ALK,	Generalized lymphadenopathy, bone marrow in 25% less common variant translocations involving ALK
T-lymphoblastic lymphoma	Lymphoblastic lymphoma	T lymphoblasts (TdT, CD2, CD3, CD7, CD4, CD8)	Mediastinal mass, bone marrow
B-lymphoblastic lymphoma	Lymphoblastic lymphoma	B lymphoblasts (CD19, CD79a, CD22, CD10, TdT)	Skin, soft tissue, bone, lymph nodes, bone marrow
Paediatric-type follicular lymphoma	Mature B Cell lymphoma	Mature B-cell	Nodal (typically head and neck). Lymphoproliferative disease associated with immunodeficiency
Paediatric nodal marginal zone lymphoma	Mature B Cell lymphoma	Mature B-cell	Nodal (typically head and neck), Lymphoproliferative disease associated with immunodeficiency

The most common pediatric non-Hodgkin lymphoma (NHL) subtypes are Burkitt lymphoma (45%), lymphoblastic lymphoma (35%), T cell or B-cell lymphoma, and anaplastic large cell lymphoma (10%), all of which are high-grade. Less common subtypes include follicular lymphoma and marginal zone lymphoma, accounting for approximately 7% of cases.[11][1]

A higher risk of NHL is associated with both congenital and acquired immunodeficiency syndromes. Congenital immunodeficiencies that are linked to NHL include Wiskott-Aldrich syndrome, ataxia telangiectasia, X-linked lymphoproliferative syndrome, and common variable immunodeficiency, and they can have a substantial impact on treatment choices.[11]

Treatments

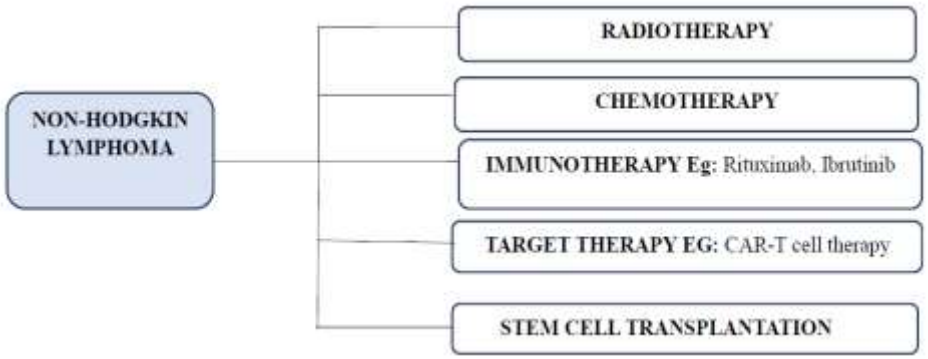

Table no. 4: Treatment of different types of NHL in children.[12]

NHL Type	Frequency of Occurrence in Pediatric NHLs and subclass	Classical Treatment	Treatment after Lack of Response to Classical Treatment or Relapse	Novel Treatment Options
Mature B-cell NHL	86% BL, BLL, LBCL, DLBCL, PMBCL, Paediatric-type follicular lymphoma, Paediatric nodal marginal zone lymphoma	Rituximab, prednisone vincristine, methotrexate doxorubicin, arabinoside cyclophosphamide, etoposide	Ibrutinib mega chemotherapy +allogenic hematopoietic stem-cell transplantation	1.monoclonal antibodies: (Obinutuzumab) 2.antibody–drug conjugates:(Inotuzumab) 3.CAR-T cell therapy 4. immune checkpoint inhibitors:(pembrolizumab) 5. pathway inhibitors:

				(buparlisib, ibrutinib)
Lymphoblastic lymphoma	1–4 years old 40% 15–19 years old 20% T-lymphoblastic lymphoma B-lymphoblastic lymphoma	CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)	chemotherapy with nelarabine, cyclophosphamide and etoposide mega chemotherapy + auto/ allogenic hematopoietic stem-cell transplantation	Ruxolitinib tyrosine-serotonin kinase inhibitors gamma secretase inhibitors
anaplastic large cell lymphoma	ALK-positive large B-cell lymphoma	doxorubicin-containing polychemotherapy, typically CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) **3-week induction therapy** (vincristine, prednisone, cyclophosphamide, daunomycin, asparaginase) followed by **a 3-week consolidation period** (vincristine, prednisone, etoposide, 6-thioguanine, cytarabine, asparaginase, methotrexate), subsequently **6 courses of maintenance chemotherapy** (cyclophosphamide, 6-thioguanine, vincristine, prednisone, asparaginase, methotrexate, etoposide, cytarabine) at 7-week intervals high-dose chemotherapy supported by **autologous stem cell transplantation**	High-dose chemotherapy supported by autologous stem cell transplantation. Allogenic stem cell transplantation	Crizotinib Crizotinib + multiagent chemotherapy ceritinib, brentuximab vedotin

Newer approaches

Monoclonal Antibodies (mAbs) Therapy

Monoclonal antibodies work by targeting specific markers on cancer cells and activating the patient's immune system, thereby reducing non-specific cytotoxic effects. Their mechanisms of action include inducing apoptosis, binding to membrane receptors on the tumor cell surface to inhibit signal transduction pathways, and facilitating both antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Table no. 5: mAbs used in NHL therapy in children.[12][13][14]

Mabs name	Generation	Target	Antigen
Rituximab	I	B Cells	Anti-CD20
Obinutzumab	II		
Ofatumumab	I		
Ublituximab	I		
Tafasitamab	II		Anti-CD19
Inebilizumab	Next generation		
Epratuzumab	Next generation		Anti-CD22
Blinatumomab	Next generation	T Cells	Anti-CD19 CD3
Mosunetuzumab	Next generation		Anti-CD20 CD3
Glofitamab	Next generation		
Odronextamab	Next generation		
Epcoritamab	Next generation		

Antibody–Drug Conjugates (ADCs)

Antibody-drug conjugates (ADCs) consist of a monoclonal antibody (mAb) linked to a small cytotoxic molecule. Their mechanism of action involves binding to cell-surface antigens on cancer cells, followed by internalization of the ADC. Once inside the cell, the cytotoxic agent is released, leading to cell cycle arrest and apoptosis. This targeted approach allows for the preferential release of potent cytotoxins in the tumor microenvironment, facilitated by proteases or pH alterations, and may also cause bystander killing of neighboring tumor cells.[12][15]

An example of an ADC is brentuximab, which combines an anti-CD30 antibody with the anti-microtubule agent monomethyl auristatin E (MMAE). This combination disrupts mitosis, resulting in cell death. Reported adverse effects include pyrexia, neutropenia, and nausea, with a safe dosage estimated at 1.8 mg/kg. Another ADC, polatuzumab vedotin, functions as a microtubule inhibitor and is currently under trial in patients aged 12–70 with B-cell non-Hodgkin lymphoma (B-NHL) or Hodgkin lymphoma who have undergone prior autologous stem-cell transplantation (auto-SCT).

Chimeric Antigen Receptor T Cell (CAR-T Cell) Therapy

CAR-T cell treatment employs T cells, which are engineered with synthetic chimeric antigen receptors (CAR). Major Histocompatibility Complex molecules are not necessary for the CAR-T cell to identify and destroy particular cancer cells.[16]

Among other things, this therapy targets the B-cell antigens CD19, CD20, and CD22, which are prominently expressed in a variety of B-cell cancers. As a result, healthy B-cells are unfortunately eliminated. B-cell maturation antigen (BCMA) is therefore utilized as a substitute target for CAR-T cell therapy. The light chain κ/λ of malignant b cells and plasma cells both express BCMA.[12] A second-generation CD19 CAR-T, tisagenlecleucel enhances CAR-T persistence, proliferation, and cytokine production. It is very active in children.[12]

DNA Methyl transferase (DNMT) inhibitors

DNA Methyl transferase (DNMT) inhibitors are enzymes that catalyse DNA methylation. DNMT inhibitors disrupt the cell cycle and proliferation, leading to differentiation and death. The molecular processes by which DNMT inhibitors elicit anti-cancer actions are partially mediated by DNA hypomethylation, which, at greater quantities, can cause cytotoxicity. The decitabine -primed CAR-T cells can detect and kill the CD19 negative malignant cells, which leads to death of lymphoma tumour cells. Decitabine increases tumour antigens and human leukocyte antigen expression, improves antigen processing, promotes T cell infiltration, and boosts effector T cell function, making it suitable for use in paediatric patients with DLBCL, high grade B-cell lymphoma, and other aggressive B-cell lymphomas. Decitabine is also reported to be beneficial in treating R/R T-lymphoblastic lymphoma in adults over the age of 14.[12]

Isocitrate Dehydrogenase (IDH) Inhibitors

IDH is an enzyme that converts isocitrate into α-ketoglutarate (αKG). Mutations related to these dehydrogenases have recently received a lot of attention because they are seen in a variety of malignancies. Mutations in IDH1/2 may result in both enzyme function loss and increased activity. They disrupt the oxidative decarboxylation of isocitrate to α-KG and increase enzymatic activity, reducing α-KG to the oncometabolite D-2-hydroxyglutarate (D-2HG). There have been reports of IDH mutations in angioimmunoblastic lymphomas (NHLs). Due to the incidence of mutant IDH in malignancies, attempts were made to create IDH inhibitors. Currently, IDH inhibitors include enasidenib, ivosidenib (AG-120), AG-881, FT2102, and IDH-305.

Oral selective inhibitors of mutant IDH, enasidenib and ivosidenib block IDH2 and IDH1, respectively.

Anaplastic Lymphoma Kinase (ALK) Inhibitors

Approximately 90% of paediatric ALK+ ALCL is caused by chromosomal translocation, which results in the formation of the oncogenic fusion protein nucleophosmin, which activates a number of pathways related to survival and proliferation. ALK is one of the targets of customized therapeutics since the survival and proliferation of ALK-transformed cells depend on ALK tyrosine kinase activity.

Crisotinib is an ALK inhibitor of the first generation. Crisotinib's toxicity, efficacy, and tolerance as a single treatment were used to show that the chemical in question works in concert with chemotherapy. Despite having a stronger affinity for ALK than crisotinib, the second-generation ALK inhibitor certinib has serious side effects that restrict its usage in children and teenagers.

BTK (bruton tyrosine kinase) inhibitors

BTK can be observed in B-cells, bone marrow cells, mast cells, and platelets. This kinase, as a critical component of the B-cell antigen receptor (BCR) signaling cascade, plays a role in all stages of B-cell development. However, if its action is unchecked, it causes uncontrolled proliferation, differentiation, and subsequent B-cell survival, resulting in the development of cancer. BTK expression has been documented in B-cell leukemias and lymphomas.

These medications come in several generations. Ibrutinib, a first-generation BTK inhibitor, is taken orally. It binds irreversibly to a cysteine residue (C481) in the active site of BTK, blocking B-cell receptor activation. As a result, it inhibits cell proliferation, survival, adhesion, and migration.

It can cause typical adverse effects such as diarrhoea, nausea, and shortness of breath. Furthermore, there have been reports of thrombocytopenia, haemorrhage, and atrial fibrillation. As a result, a second generation of BTK inhibitors has been created, which includes acalabrutinib, zanubrutinib, and tirabrutinib. These inhibitors, while comparable to ibrutinib, bind covalently to the C481 residue in BTK, resulting in greater target selectivity. It is probable that this will lessen the frequency of negative effects, especially cardiovascular ones. Currently, the FDA has approved acalabrutinib and zanubrutinib for therapy.

Inhibitor of proteasome

Bortezomib is a derivative of peptide aldehyde. In its class, it is the first powerful, reversible, and specific inhibitor of the 26S proteasome. Its function is to bind directly to the proteasome's active sites, inhibiting the ubiquitin–proteasome cascade and so preventing targeted protein proteolysis. Apoptosis and the suppression of cell cycle progression, angiogenesis, cell adhesion, and proliferation result from the dysregulation of homeostatic processes at the cellular level. Notably, bortezomib has also been demonstrated to cause apoptosis in cells that overexpress BCL2.

Additionally, bortezomib has a number of potential adverse effects. Peripheral neuropathy is the most significant of these; it often affects the feet more frequently than the hands and is sensory, distal, and symmetrical. Most of the time, it can be reversed by ceasing treatment. Furthermore, compared to intravenous dosing, subcutaneous bortezomib has been demonstrated to carry a decreased risk. Additional adverse effects that could be noted include tiredness, neutropenia, thrombocytopenia, and gastrointestinal toxicity (e.g., diarrhea or constipation). Antiviral prophylaxis is typically advised since bortezomib medication may also cause shingles to reactivate. Notably, bortezomib-induced isolated cutaneous vasculitis does not necessarily result in stopping treatment.

Common Chemotherapeutic agents used for Hodgkin and Non-Hodgkin lymphoma

Doxorubicin

Doxorubicin (DOX), a class I anthracycline chemotherapy agent derived from *Streptomyces peucetius var. caesius*, is widely used to treat various cancers, including solid tumors and haematological malignancies in both adults and children. It is particularly effective in managing Hodgkin and non-Hodgkin lymphomas as well as pediatric cancers.[31][32] DOX exerts its therapeutic effects through two primary mechanisms: intercalation into DNA, which disrupts topoisomerase-II-mediated repair, and the generation of free radicals that damage cellular membranes, DNA, and proteins.[33] While effective, DOX can induce apoptosis and necrosis in healthy tissues, leading to toxicity in the brain, liver, kidneys, and heart, with cardiotoxicity being its most prominent side effect. Renal toxicity, manifesting as nephropathy and proteinuria, is attributed to glomerular podocyte injury. Other adverse effects include cutaneous reactions such as hyperpigmentation, alopecia, itching, photosensitivity, rashes, fever, urticaria, and anaphylaxis. Gastrointestinal side effects, including vomiting and mucositis, typically occur within the first 5–10 days of treatment, with most patients recovering within 10 days. However, severe cases may involve ulceration, necrosis, and life-threatening infections in the colon and cecum.[32]

Bleomycin

Bleomycin exerts its greatest impact on neoplastic cells during the G2 phase of the cell replication cycle. While it does intercalate into DNA, its significant cytotoxic effects are primarily attributed to iron-catalyzed free radical formation and subsequent DNA strand breakage. This medication is effective in treating Hodgkin's and non-Hodgkin's lymphomas. Notably, bleomycin causes minimal myelosuppression and largely spares the bone marrow. However, its most severe toxicities are pulmonary and mucocutaneous reactions. Additional side effects include hyperpigmentation.[34]

Vinblastine

Vinblastine, a vinca alkaloid produced from the Catharanthus roseus plant, exerts its anticancer effects primarily through its action on microtubules, a vital component of the cytoskeleton involved in cell division. By disrupting microtubule dynamics, vinblastine affects the development of the mitotic spindle, resulting to cell cycle arrest in metaphase and ultimately causing death in cancer cells.[36][39] Fever, chills, nausea, vomiting, reversible myelosuppression, hepatitis, transient hypotension, congestive heart failure, renal insufficiency, nonselective proteinuria, photosensitivity reactions, and acute symptomatic hyponatremia were among the adverse effects associated with vinblastine. These effects were impacted by other host variables and persisted even when the dose was reduced.[40][41]

Vincristine

The vinca alkaloid vincristine, also called leurocristine, is a powerful chemotherapeutic drug that is used to treat cancer. It is extracted from the Catharanthus roseus plant. In order to prevent cell division and proliferation, vincristine disrupts the cell cycle by creating abnormalities in microtubule function. As an antimitotic, it prevents the mitotic spindle from forming during cell division, which results in cell cycle arrest. Because of this disruption, vincristine is an effective chemotherapeutic drug that can be used to treat a variety of cancers.[35] Vincristine's effectiveness and resistance are increased when it is combined with other chemotherapeutic drugs, such as doxorubicin and cyclophosphamide.[36] Neuropathy, numbness, tingling, muscle weakness, and altered gait are some of the symptoms of vincristine-induced peripheral neuropathy (VIPN). About 30% of patients suffer with VIPN, which can significantly affect quality of life, restrict dosage,

and postpone treatment.[37] Additionally, allergic reactions to vincristine may occur, such as Kounis-type reactions that result in an abrupt myocardial infarction.[38]

Dacarbazine

Dacarbazine is an anticancer prodrug that needs to be activated by N-demethylation in the liver. Through the production of reactive oxygen species, a reduction in mitochondrial membrane potential, and lysosomal membrane rupture, its active metabolite causes cytotoxic effects and stops the course of disease by alkylating guanine bases in DNA.[42] Anorexia, nausea, vomiting, bone marrow suppression, hepatotoxicity, influenza like syndrome, facial flushing, paraesthesia, photosensitivity reactions, and veno-occlusive illness are among the side effects of dacarbazine chemotherapy in children. Notably, there have been reports of anaphylactic shock and other hypersensitivity events.[43]

Mechlorethamine

Mechlorethamine functions as a DNA alkylating agent, creating DNA cross-links that interfere with replication and transcription, ultimately resulting in cell death. This mechanism is utilized in cancer therapy to effectively target and destroy rapidly dividing tumour cells.[44] However, mechlorethamine can cause immediate neurotoxic effects, such as confusion, headaches, hallucinations, and seizures, which commonly manifest around four days after treatment. It may also trigger hypersensitivity reactions, including urticaria and anaphylactoid symptoms.[45][46]

Etoposide

Etoposide acts by blocking topoisomerase II, an enzyme that is essential for DNA replication and repair. It is a successful chemotherapeutic drug for a variety of cancers because it causes DNA strand breaks, which in turn cause cancer cells to undergo apoptosis.[47] At a median time-to-onset of 10 days after dose, etoposide-related side effects include thrombocytopenia, leukopenia, anaemia, stomatitis, pneumonitis, and unforeseen occurrences such as thrombotic microangiopathy, ototoxicity, second primary malignancy, kidney toxic, and ovarian failure.[48][49]

Cyclophosphamide

It is a prodrug that is activated by P-450 enzymes to produce the active form phosphoamide mustard. The active medicine alkylates nucleophilic groups found on DNA bases. Specifically at the N-7 position of guanine. This causes base cross-linking, aberrant base pairing, and DNA strand breaking. Adverse consequences include alopecia, nausea, vomiting, myleosuppression, and hemorrhagic cystitis.[34]

Daunomycin

Daunomycin's mode of action in cancer therapy is intercalation with DNA, which disrupts nucleic acid synthesis and interferes with template DNA function, causing cell damage largely in the nucleus and inhibiting the growth of both normal and neoplastic cells.[50] Daunomycin's side effects include severe local reactions due to extravasation, bone marrow depression resulting in leukopenia, anaemia, thrombocytopenia, fever, oral ulcers, alopecia, and potential cardiac issues such as tachycardia and pulmonary insufficiency, especially during maintenance therapy.[51]

Asparaginase

Asparagine is deaminated to aspartic acid and ammonia salt by L-asparaginase. L-asparaginase is used in combination therapy to treat severe lymphocytic leukemia in children. Because of their restricted ability to synthesis enough asparagines to support growth and function, many neoplastic cells need an external source of this amino acid. This is the basis for its method of action. Because blood asparagines are hydrolyzed by L-asparaginase, tumor cells are deprived of this amino acid, which is essential for protein synthesis. Acute pancreatitis can be brought on by asparaginase.

6-thioguanine

6-thioguanine functions as an antimetabolite, interfering with DNA and RNA synthesis and preventing purine synthesis. Its therapeutic application in the treatment of cancer may be limited by adverse effects such as myelosuppression, hepatotoxicity, and gastrointestinal disturbances.[56]

Cytarabine

Cytarabine, an antimetabolite, inhibits DNA/RNA polymerase and nucleotide reductase enzymes, limiting the cell's ability to replicate. This process inhibits the S phase of the cell cycle, resulting in cell death in cancer therapy.[53] Cytarabine has a limited therapeutic application and is primarily used in combination with daunorubicin or thioguanine. A high dose of cytarabine can harm the liver, heart, and other organs.[34]

Methotrexate

Methotrexate, a folic acid antagonist, has a structure similar to that of folic acid. It is actively transported into mammalian cells, where it inhibits dihydrofolate reductase, an enzyme essential for converting dietary folate into tetrahydrofolate, a form required for thymidine and purine synthesis. Methotrexate is highly myelosuppressive, leading to severe leucopenia, bone marrow aplasia, and thrombocytopenia. It can also cause significant gastrointestinal disturbances. Renal toxicity may occur due to the precipitation (crystalluria) of its 7-OH metabolite.

Prednisone

Prednisone inhibits oncogenic B cell receptor signaling (BCR) in lymphomas by attaching itself to the glucocorticoid receptor. In malignant B cells, it promotes cell death by lowering BCR quantity and CSK expression, which in turn lowers kinase activity.[52]

Procarbazine

Procarbazine, an alkylating agent used in cancer therapy, is particularly effective in treating Hodgkin's lymphoma. It acts as a prodrug, requiring metabolic activation to produce intermediates that inhibit the synthesis of DNA, RNA, and proteins, thereby suppressing cancer cell proliferation.[54] Common adverse effects of procarbazine include gastrointestinal disturbances, myelosuppression, central nervous system symptoms, and neuromuscular issues. Less frequently, it may cause secondary malignancies, azoospermia, or hypersensitivity reactions, underscoring the need for careful monitoring during treatment.[54]

Cytosine arabinoside

Cytosine arabinoside (Ara-C) works by incorporating into DNA and replacing deoxycytidine triphosphate, which ultimately leads to cell death. Its adverse effects include myelosuppression, characterized by granulocytopenia, anemia, and thrombocytopenia, caused by damage to both hematopoietic and stromal cells in the bone marrow.[55]

CONCLUSION

Pediatric lymphoma is a highly treatable cancer, with cure rates surpassing 80% for many subtypes. Advances in risk-adapted strategies, targeted therapies, and immunotherapies have greatly enhanced outcomes for children with lymphoma. Despite these achievements, managing pediatric lymphoma remains complex and necessitates a multidisciplinary approach. Emerging treatments, such as CAR-T cell therapy and personalized medicine, offer promising avenues for future advancements in care.

REFERENCES

1. Guja KE, Nadel H, Iagaru A. Overview and recent advances in 18F-FDG PET/CT for evaluation of pediatric lymphoma. InSeminars in Nuclear Medicine, 2023; 1, 53, (3): 400-412.
2. von der Weid NX. Adult life after surviving lymphoma in childhood. Supportive Care in Cancer, 2008; 16: 339-45.
3. Chamba C, Mawalla W. The future of lymphoma diagnosis, prognosis, and treatment monitoring in countries with limited access to pathology services. InSeminars in Hematology, 2023; 1.
4. Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. New England Journal of Medicine, 1996; 9, 334(19): 1238-48.
5. Voss SD, Cairo MS. Surveillance imaging in pediatric lymphoma. Pediatric Radiology, 2019; 49(11): 1565-73.
6. Omar FE. Childhood Lymphomas–a brief overview. Continuing Medical Education, 2010; 28(7): 332-6
7. Steliarova-Foucher E, Colombet M, Ries LA, Moreno F, Dolya A, Bray F, Hesseling P, Shin HY, Stiller CA, Bouzbid S, Hamdi-Cherif M. International incidence of childhood cancer, 2001–10: a population-based registry study. The Lancet Oncology, 2017; 1, 18(6): 719-31.
8. Nagpal P, Akl MR, Ayoub NM, Tomiyama T, Cousins T, Tai B, Carroll N, Nyrenda T, Bhattacharyya P, Harris MB, Goy A. Pediatric Hodgkin lymphoma–biomarkers, drugs, and clinical trials for translational science and medicine. Oncotarget, 2016; 10, 7(41): 67551.
9. Mauz-Körholz C, Metzger ML, Kelly KM, Schwartz CL, Castellanos ME, Dieckmann K, Kluge R, Körholz D. Pediatric hodgkin lymphoma. Journal of Clinical Oncology, 2015; 20, 33(27): 2975-85.
10. Oberlin O, Faranoush M. Pediatric Non-Hodgkin's Lymphomas. Iranian J Blood Cancer, 2010; 1, 3: 107-2.
11. Britto TI, Fattah SA, Rahman MA, Chowdhury MA. A Systematic Review on Childhood Non-Hodgkin Lymphoma: An Overlooked Phenomenon in the Health and Research Sector of Bangladesh. Cureus, 2023; 15(9).
12. Derebas J, Panuciak K, Margas M, Zawitkowska J, Lejman M. The new treatment methods for non-hodgkin lymphoma in pediatric patients. Cancers, 2022; 18, 14(6): 1569.
13. Baldo, B.A. Monoclonal antibodies approved for cancer therapy. Saf. Biol. Ther, 2016; 57–140.
14. Salvaris R, Ong J, Gregory GP. Bispecific antibodies: a review of development, clinical efficacy and toxicity in B-cell lymphomas. Journal of Personalized Medicine, 2021; 29, 11(5): 355.
15. Chu Y, Zhou X, Wang X. Antibody-drug conjugates for the treatment of lymphoma: clinical advances and latest progress. Journal of Hematology & Oncology, 2021; 5, 14(1): 88.
16. Zhao Z, Chen Y, Francisco NM, Zhang Y, Wu M. The application of CAR-T cell therapy in hematological malignancies: advantages and challenges. Acta Pharmaceutica Sinica B, 2018; 1, 8(4): 539-51.
17. Ansell SM. Hodgkin lymphoma: 2016 update on diagnosis, risk-stratification, and management. American journal of hematology, 2016; 91(4): 434-42.
18. De Re V, Repetto O, Mussolin L, Brisotto G, Elia C, Lopci E, d'Amore ES, Burnelli R, Mascarin M. Promising drugs and treatment options for pediatric and adolescent patients with Hodgkin lymphoma. Frontiers in Cell and Developmental Biology, 2022; 24, 10: 965803.
19. Gómez-Almaguer D, González-Llano O, Jiménez-Antolinez V, Gómez-De León A. Treatment of classical Hodgkin's lymphoma in children and adolescents. Expert Opin Pharmacother, 2019; 20(10): 1227-1234.
20. Hall MD, Terezakis SA, Lucas JT, Gallop-Evans E, Dieckmann K, Constine LS, Hodgson D, Flerlage JE, Metzger ML, Hoppe BS. Radiation therapy across pediatric Hodgkin lymphoma research group protocols: a report from the Staging, Evaluation, and Response Criteria Harmonization (SEARCH) for

Childhood, Adolescent, and Young Adult Hodgkin Lymphoma (CAYAHL) Group. International Journal of Radiation Oncology* Biology* Physics, 2022; 1, 112(2): 317-34.
21. McKenna RW, Kyle RA, Kuehl WM, Grogan TM, Harris NL, Coupland RW. WHO classification of tumours of haematopoietic and lymphoid tissues. Plasma cell neoplasms. Lyon: IARC, 2008; 200-13.
22. Al-Rahawan MM, De Alarcón PA. Gemcitabine and vinorelbine therapy for patients with Hodgkin lymphoma. Pediatric Health, 2009; 1, 3(6): 525-32.
23. Shankar A, Visaduraki M, Hayward J, Morland B, McCarthy K, Hewitt M. Clinical outcome in children and adolescents with Hodgkin lymphoma after treatment with chemotherapy alone–The results of the United Kingdom HD3 national cohort trial. European journal of cancer, 2012; 1, 48(1): 108-13.
24. Ng AK, Mauch PM. Late effects of Hodgkin's disease and its treatment. The Cancer Journal, 2009; 1, 15(2): 164-8.
25. Cole PD, Schwartz CL, Drachtman RA, De Alarcon PA, Chen L, Trippett TM. Phase II study of weekly gemcitabine and vinorelbine for children with recurrent or refractory Hodgkin's disease: a children's oncology group report. Journal of Clinical Oncology, 2009; 20, 27(9): 1456-61.
26. Gobbi PG, Ferreri AJ, Ponzoni M, Levis A. Hodgkin lymphoma. Critical reviews in oncology/hematology, 2013; 1, 85(2): 216-37.
27. Bonadonna G, Santoro A. ABVD chemotherapy in the treatment of Hodgkin's disease. Cancer Treatment Reviews, 1982; 1, 9(1): 21-35.
28. Schwartz CL, Constine LS, Villaluna D, London WB, Hutchison RE, Sposto R, Lipshultz SE, Turner CS, DeAlarcon PA, Chauvenet A. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate-and high-risk Hodgkin lymphoma: the results of P9425. Blood, The Journal of the American Society of Hematology, 2009; 3, 114(10): 2051-9.
29. Mauz-Körholz C, Hasenclever D, Dörffel W, Ruschke K, Pelz T, Voigt A, Stiefel M, Winkler M, Vilser C, Dieckmann K, Karlén J. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. Journal of clinical oncology, 2010; 10, 28(23): 3680-6.
30. Metzger ML, Link MP, Billett AL, Flerlage J, Lucas Jr JT, Mandrell BN, Ehrhardt MJ, Bhakta N, Yock TI, Friedmann AM, de Alarcon P. Excellent outcome for pediatric patients with high-risk Hodgkin lymphoma treated with brentuximab vedotin and risk-adapted residual node radiation. Journal of Clinical Oncology, 2021; 10, 39(20): 2276-83.
31. Micallef I, Baron B. Doxorubicin: An overview of the anti-cancer and chemoresistance mechanisms. Isaac Micallef, Byron Baron* Centre for Molecular Medicine and Biobanking, University of Malta, Malta, 2020; 23.
32. Tacar O, Sriamornsak P, Dass CR. Doxorubicin: an update on anticancer molecular action, toxicity and novel drug delivery systems. Journal of pharmacy and pharmacology, 2013; 65(2): 157-70.
33. Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, McLeod H, Klein TE, Altman RB. Doxorubicin pathways: pharmacodynamics and adverse effects. Pharmacogenetics and genomics, 2011; 1, 21(7): 440-6.
34. Anupam S, Deep AA, Arti D, Mahindra A. A Review on Antineoplastic Agent. International Journal of Advances in Engineering and Management (IJAEM), 2020; 2(5): 827-838.
35. Garg N, Farhat J, Dhankhar S, Chauhan S, Bala R, Madaan R, Sharma H, Saini M, Singh TG, Aldahish AA, Almarhoon Z. Vincristine in cancer therapy: mechanisms, efficacy, and future perspectives. Current medicinal chemistry, 2024.
36. Verma V, Sharma S, Gaur K, Kumar N. Role of vinca alkaloids and their derivatives in cancer therapy. World Journal of Advanced Research and Reviews, 2022; 16(3): 794-800.
37. Hu YH, Li GZ, Long JY, Yang QY, Zhang Y, Chen F, Wang YR. Severe Vincristine-Induced Neuropathic Pain: A Case Report with Pharmacogenetic Analysis and Literature Review. Pharmacogenomics and Personalized Medicine, 2022; 31: 1029-35.
38. Hill DA, Leahy AB, Sciasci J, O'Neill SP, Reilly A, Balamuth N, Seeholzer SH, Spergel JM, Brown-Whitehorn TF. Reply to: Medication contaminants as a potential cause of anaphylaxis to vincristine. What about drug specific antigens? Pediatric blood & cancer, 2017; 19, 65(2): 10-02.
39. González-Burgos E, Gómez-Serranillos MP. Vinca alkaloids as chemotherapeutic agents against breast cancer. Discovery and development of anti-breast cancer agents from natural products, 2021; 1: 69-101.
40. Bennett CL, Vogelzang NJ, Ratain MJ, Reich SD. Hyponatremia and Other Toxic Effects During a Phase I Trial of Recombinant Human Gamma Interferon and Vinblastine¹, 2. Cancer treatment reports, 1986; 70(9): 1081.
41. Breza TS, Halprin KM, Taylor JR. Photosensitivity reaction to vinblastine. Archives of Dermatology, 1975; 1, 111(9): 1168-70.
42. Amirmostofian M, Jaktaji JP, Soleimani Z, Tabib K, Tanbakosazan F, Omrani M, Kobarfard F. Synthesis and molecular-cellular mechanistic study of pyridine derivative of dacarbazine. Iranian journal of pharmaceutical research: IJPR, 2013; 12(3): 255.
43. ABHYANKAR S, RAO SP, POLLIO L, MILLER ST. Anaphylactic shock due to dacarbazine (NSC 45388). American Journal of Diseases of Children, 1988; 1, 142(9): 918.
44. Cao Y, Pan R, Xuan W, Wei Y, Liu K, Zhou J, Wang W. Photo-triggered fluorescent theranostic prodrugs as DNA alkylating agents for mechlorethamine

release and spatiotemporal monitoring. Organic & Biomolecular Chemistry, 2015; 13(24): 6742-8.
45. Sullivan KM, Storb R, Shulman HM, Shaw CM, Spence A, Beckham C, Clift RA, Buckner CD, Stewart P, Thomas ED. Immediate and delayed neurotoxicity after mechlorethamine preparation for bone marrow transplantation. Annals of Internal Medicine, 1982; 1, 97(2): 182-9.
46. Daughters D, Zackheim H, Maibach H. Urticaria and anaphylactoid reactions: After topical application of mechlorethamine. Archives of Dermatology, 1973; 1, 107(3): 429-30.
47. Bailly C. Etoposide: a rider on the cytokine storm. Cytokine, 2023; 1, 168: 156234.
48. Cui Z, Cheng F, Wang L, Zou F, Pan R, Tian Y, Zhang X, She J, Zhang Y, Yang X. A pharmacovigilance study of etoposide in the FDA adverse event reporting system (FAERS) database, what does the real world say?. Frontiers in Pharmacology, 2023; 26, 14: 1259908.
49. Singaraju M, Palaian S, Shankar PR, Shrestha S. Safety profile and toxicity amelioration strategies of common adverse effects associated with anticancer medications. J Pharm Res Int, 2020; 32(11): 18-30.
50. Di Marco A, Arcamone F, Zunino F. Daunomycin (daunorubicin) and adriamycin and structural analogues: biological activity and mechanism of action. InMechanism of action of antimicrobial and antitumor agents, 1975; 1: 101-128.
51. Tan C, Tasaka H, Yu KP, Murphy ML, Karnofsky DA. Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease. Clinical evaluation with special reference to childhood leukemia. Cancer, 1967; 20(3): 333-53.
52. Choi J, Ceribelli M, Phelan JD, Häupl B, Huang DW, Wright G, Hsiao T, Morris VM, Ciccarese F, Wang B, Corcoran SR. Molecular Mechanism of Action of Glucocorticoids in Lymphoma Therapy. Blood, 2023; 2, 142(1): 2986
53. Salehi B, Selamoglu Z, S. Mileski K, Pezzani R, Redaelli M, C. Cho W, Kobarfard F, Rajabi S, Martorell M, Kumar P, Martins N. Liposomal cytarabine as cancer therapy: from chemistry to medicine. Biomolecules, 2019; 23, 9(12): 773.
54. Armand JP, Ribrag V, Harrousseau JL, Abrey L. Reappraisal of the use of procarbazine in the treatment of lymphomas and brain tumors. Therapeutics and clinical risk management, 2007; 30, 3(2): 213-24.
55. Teleka S, Chijuwa A, Senga E, Chisi JE. Cytosine Arabinoside reduces the numbers of granulocyte macrophage colony forming cells (GMCFC) and high proliferative potential colony forming cells (HPP-CFC) in vivo in mice. Malawi Medical Journal, 2011; 23(4): 119-22.
56. Grem JL, Keith B. Mechanism of action of cancer chemotherapeutic agents: antimetabolites. The cancer handbook, 2005; 15.