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Hodgkin's disease – Not Unknown Disease

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Abstract

Hodgkin's Lymphoma (HL) is a distinctive and highly manageable lymphoid neoplasm predominantly affecting the young adult population. In recent years, significant strides have been taken in comprehending the molecular underpinnings of HL and the development of innovative therapeutic modalities. This abstract provides an overview of recent advances in Hodgkin's Lymphoma treatment, with a focus on promising therapeutic strategies and approaches. Advances in elucidating the molecular and genetic underpinnings of HL have led to the identification of novel therapeutic targets. Immune checkpoint inhibitors, including Pembrolizumab and Nivolumab, have demonstrated remarkable efficacy in cases of relapsed or refractory HL by reactivating the host's immune response against malignant cells. Combinatorial approaches involving these agents and traditional chemotherapy have exhibited even more encouraging results. Additionally, the advent of targeted therapies such as Brentuximab vedotin, which selectively delivers cytotoxic payloads to CD30 – expressing Hodgkin's Lymphoma cells, has significantly enhanced treatment outcomes. Brentuximab vedotin, when employed in conjunction with chemotherapy, has emerged as a standard –of- care first – line treatment option for numerous HL patients. In recent years, endeavours to mitigate the long – term sequelae of treatment have garnered prominence. Reduced – intensity radiation therapy and less toxic chemotherapeutic regimens have been explores to curtail the risk of secondary malignancies and other treatment – related complications. This approach seeks to uphold high remission rates while concurrently enhancing the quality of life for HL survivors. In summation, recent therapies strides in HL have ushered in a new era of optimism for patients. Immunotherapy, targeted therapies, and strategies to ameliorate treatment – associated adverse events have collectively enhanced the prognosis for individuals with HL. Ongoing research and clinical trials continue to refine treatment paradigms, holding the promise of further improvements in outcomes in the foreseeable future.

Abbreviations:

HL - Hodgkin's Lymphoma

CD30 - also known as TNFRF8 (Tumor Necrosis factor receptor super-family member 8.

cHL - Classical Hodgkin's Lymphoma

PD -1 - Programmed Cell Death Protein 1

TLS - Tumor Lysis Syndrome

ALCL - Anaplastic large cell lymphoma

ADC - Antibody drug conjugate

MMAE - Mono methyl auristastin E

IV - Intravenous

IM - Intramuscular

FDA - Food and Drug Administration

DLBCL - Diffuse large B - cell lymphoma

T - cells - T lymphocytes (Thymus - dependent development)

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DNA - Deoxyribonucleic acid

ABVD - A: Doxorubicin (Adriamycin), B: Bleomycin, V: Vinblastine, D: Dacarbazine.

Introduction

Hodgkin's lymphoma (HL) represents a distinctive malignancy within the realm of hematological neoplasms. First described by Dr. Thomas Hodgkin in the 19th century, it has since evolved from an enigmatic entity into a well - characterized disease, thanks to extensive research efforts. The review article aims to provide a comprehensive overview of Hodgkin's lymphoma, integrating recent advances in etiology, pathogenesis, and therapeutic strategies, with a focus on seminal studies and breakthroughs.

Hodgkin's lymphoma is a heterogeneous disorder predominantly affecting young adults. It is characterized by the presence of Reed - Sternberg cells and their variants within the lymphoid tissue. Over the years, refined diagnostic criteria have emerged, leading to improved classification system, most recently updates in 2016, has contributes to a more precise categorization of Hodgkin's lymphoma subtypes, enabling tailored therapeutic approaches.

The etiology of Hodgkin's lymphoma is complex and multi factorial. Genetic predisposition, environmental factors, and viral infections have all been implicated. Recent genetic studies have shed light on specific alternations, such as copy number variations and gene mutations, contributing to lymphomagenesis(1). Additionally, the role of the Epstein - Barr virus (EBV) in a subset of cases has been well - established (2).

Treatment strategies for Hodgkin's lymphoma have evolved significantly over the past few decades. Traditionally, a combination of chemotherapy and radiation therapy has been the standard care, resulting in high cure rates. However, these therapies are associated with substantial long - term toxicities. Advances in precision medicine have ushered in a new era of therapy, with targeted agents and immunotherapies gaining prominence. The PD-1 inhibitor pembrolizumab, for instance, has demonstrated remarkable efficacy in relapsed/refractory cHL (3).

Personalized medicine has become increasingly relevant in HL management. Molecular Profiling, including next - generation sequencing, allows for the identification of specific mutations and molecular markers, guiding treatment decisions (4). Furthermore, risk - adapted approaches have been developed to optimize therapeutic outcomes while minimizing adverse effects particularly in early - stage HL (5).

Challenges in Hodgkin's lymphoma represents a captivating model of malignancy, where scientific progress has transformed our understanding and management of the disease. This review will synthesize current knowledge about Hodgkin's lymphoma, encompassing its etiology, classification, diagnostic advances, and evolving therapeutic options, with reference to key studies and pivotal discoveries. By amalgamating recent research findings, this review endeavors to contribute to the collective knowledge base, ultimately improving the care and outcomes of individuals affected by Hodgkin's lymphoma.

Key Characteristics of Hodgkin's lymphoma include:-

- Presence of specific abnormal cells called 'Reed - Sternberg cells within affected lymph nodes.
- These cells, along with other cell types, make up the characteristic cellular makeup of this disease.

Hodgkin's lymphoma is categorized into two main types:-

Classical Hodgkin Lymphoma:- This is the most common form of Hodgkin's lymphoma and is further divided into subtypes, including nodular sclerosis, mixed cellularity, lymphocyte - rich, and lymphocyte - depleted. Each subtype has distinct characteristics, but they all involve the presence of Reed - Sternberg cells.

Nodular Lymphocyte - Predominant Hodgkin's Lymphoma:- This is a less common subtype of Hodgkin's lymphoma and is characterized by the presence of popcorn cells, which are large lymphoma cells with multiple nuclei.

Symptoms of Hodgkin's Lymphoma can vary but may include:-

- Painless swelling of lymph nodes, typically in the neck, axillary, or groin.
- Fever and chills
- Night sweats
- Unexplained weight loss
- Fatigue
- Itchy skin
- Anorexia
- Pain in lymph nodes after consuming alcohol (Rare).

The exact cause of Hodgkin's lymphoma is unknown, but it is thought to be related to genetic and environmental factors. It can affect people of all ages; although it is most commonly diagnosed in young adults (ages 15 to 35) and older adults (ages 55 and older).

Treatment for Hodgkin's lymphoma typically involves a combination of therapies including chemotherapy, radiation therapy, and in some cases, stem cell transplantation. The choice of treatment depends on the stage of the disease,

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the subtype, and the patient's overall health.

Prognosis for Hodgkin's lymphoma is generally favourable, with a high rate of cure, especially in early - stage cases. Advances in treatment and research continue to improve outcomes and reduce long - term side effects for those affected by this cancer(6).

Hyperuricemia is not directly related to Hodgkin's lymphoma, but it can be associated with this type of cancer due to certain factors and complications.

Hyperuricemia is a medical condition characterized by elevated levels of uric acid in the blood. Uric acid is a waste product that is normally excreted by the kidneys. When uric acid levels become too high, it can lead to the formation of uric acid crystals, which can accumulate in joints and other tissues, causing gout or kidney stones(7).

In the context of Hodgkin's lymphoma, hyperuricemia may occur as a result of several factors:

Tumor Lysis Syndrome (TLS):- Hodgkin's lymphoma, like other cancers, can sometimes lead to a condition called tumor lysis syndrome. TLS occurs when cancer cells break down rapidly, releasing their contents into the blood stream. This can lead to a surge in the release of uric acid, which can overwhelm the kidney's ability to excrete it, resulting in hyperuricemia.

Chemotherapy and Radiation Therapy:- Treatment for Hodgkin's lymphoma often involves chemotherapy and radiation therapy. These treatments can also cause cancer cells to break down rapidly, leading to TLS an increase in uric acid levels.

Impaired Kidney Function:- Some individuals with Hodgkin's lymphoma may have impaired kidney function due to the disease itself or as a side effect of treatment. If the kidneys are not functioning optimally, they may have difficulty excreting uric acid, leading to hyperuricemia.

Anemia can be related to Hodgkin's lymphoma in several ways:

A. Bone Marrow Involvement,

B. Chemotherapy and Radiation therapy,

C. Inflammatory Response,

D. Malnutrition,

E. Blood loss

It is important to note that anemia in individuals with Hodgkin's lymphoma can vary in severity and may be temporary or chronic(8). Anemia can cause symptoms such as fatigue, weakness, pale skin, and shortness of breath,which can impact a person's quality of life. Management of anemia in Hodgkin's lymphoma patients may involve treating the underlying cancer, addressing nutritional deficiencies, and providing supportive care such as blood transfusions or medications to stimulate red blood cell production(9,10).

Brentuximab Vedotin:

On November 10,2022 the FDA approved Brentuximab vedotin in combination with doxorubicin, vincristine, etoposide, prednisone and cyclophosphamide for pediatric patients two years of age and older with previously untreated high risk classical Hodgkin lymphoma (cHL).

Brentuximab vedotin it is used to treat types of cancer, primarily Hodgkin Lymphoma and systemic anaplastic large cell lymphoma (ALCL). It is classified as an antibody - drug conjugate (ADC) and is designed to specifically target cancer cells while minimizing damage to healthy cells.

Mechanism of Action:

Brentuximab vedotin consists of two main components - a monoclonal antibody and a cytotoxic agent. The antibody part of the drug is designed to recognize and bind to a protein called CD30, which is found on the surface of certain cancer cells, particularly in Hodgkin Lymphoma and ALCL. Once the antibody attaches to CD30, the entire molecule is taken up by the cancer cell.

Intracellular Delivery:

Once inside the cancer cell, Brentuximab vedotin releases its cytotoxic payload, a substance called monomethyl auristatin E (MMAE). MMAE disrupts the cell's micro tubules, which are crucial for cell division and growth. This disruption leads to cell cycle arrest and ultimately cell death.

Indications:

Brentuximab vedotin is primarily used in the treatment of 2 main types of lymphomas:-

- Classical Hodgkin lymphoma (cHL): Especially in cases where the cancer has relapsed after previous treatment or when stem cell transplantation is not a viable option.
- Systemic anaplastic large cell lymphoma (ALCL): Specifically in cases where the cancer has either relapsed or become refractory to other treatments.

Administration:

Brentuximab vedotin is typically administered by intravenous (IV) infusion, usually every few weeks. The

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specific dosing schedule and duration of treatment may vary based on the individual patient and the stage of their disease.

Side Effects:

- Fatigue
- Nausea
- Diarrhea
- Peripheral neuropathy
- Low white blood cell counts
- Severe allergic reactions

Precautions:

Patients should inform their healthcare provider of any allergies, other medical conditions, or medications they are taking. It's important to discuss potential side effects and the benefits of the treatment with the healthcare team.

Glofitamab:

On July 10, 2023 The FDA recently approved glofitamab to treat adults with diffuse large B- cell lymphoma (DLBCL) or large B-cell lymphoma arising from follicular lymphoma, whose disease has not responded relapsed after two prior therapies.

Mechanism of Action:

Glofitamab is classified as a bi-specific T-cell engager (BiTE) antibody. It is designed to bind to both CD20, a protein found on the surface of B-cell lymphoma cells, and CD3, a protein found on T-cells, glofitamab brings these two cell types into close proximity, which helps to activate the T- cells and stimulate them to attack and kill the cancer cells.

Targeted Indications:

Glofitamab was being investigated for the treatment of various B-cell malignancies, including (DLBCL) and follicular lymphoma, among others.

Potential Advantages:

Bi-specific antibodies like glofitamab are designed to harness the power of immune system to specifically target cancer cells, potentially leading to fewer side effects compared to traditional chemotherapy.

Bleomycin Sulfate:

It is classified as an anti neoplastic antibiotic and is used as part of combination chemotherapy regimens of various malignancies, including testicular cancer, Hodgkin's lymphoma, and some types of non - small cell lung cancer.

Mechanism of Action:

Bleomycin works by interfering with DNA synthesis and replication in rapidly dividing cells, including cancer cells. It induces DNA strand break and other damage, ultimately leading to cell death. Unlike many chemotherapy drugs, bleomycin does not primarily affect actively dividing bone marrow cells, which is why it is often used in combination with other drugs in chemotherapy regimens.

Indications:

Hodgkin's Lymphoma - Part of the ABVD (Doxorubicin, bleomycin, vinblastine, and dacarbazine).

Administration:

Bleomycin is typically administered intravenously (IV) in a healthcare setting, such as a hospital or clinic. It may also be given intramuscularly (IM) in certain cases.

Side Effects:

- Pulmonary toxicity results in lung damage,
- Cough
- Dyspnea
- Lung inflammation
- Skin reactions,
- Fever
- Chills
- Low white blood cell counts.

Precautions:

Patients with pre-existing lung conditions or a history of lung disease may be at higher risk for bleomycin - induced pulmonary toxicity. Careful monitoring and assessment of lung function are essential during treatment.

Contraindications:

Bleomycin is generally not recommended for pregnant individuals due to potential harm to the fetus.

Conclusion

This review article has provided a comprehensive overview of Hodgkin's lymphoma, a malignancy that continues to challenge both patients and healthcare providers. Through an examination of the latest research and clinical advancements, several key themes have emerged:

1. **Improved Understanding of Pathogenesis**:- Advances in molecular biology and genetics have deepened our understanding of the underlying causes of Hodgkin's lymphoma, paving the way for targeted therapies and

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precision medicine approaches.

2. **Treatment Paradigm Shift**:- The landscape of Hodgkin's lymphoma treatment has evolved significantly, with a greater emphasis on risk stratification, reduced toxicity, and improved outcomes. The integration of chemotherapy, radiation therapy, immunotherapy, and stem cell transplantation has revolutionized patient care.

3. **Immunotherapy Revolution**:- The emergence of immune checkpoint inhibitors, such as Pembrolizumab and Nivolumab, has demonstrated remarkable efficacy in relapsed or refractory Hodgkin's lymphoma, offering renewed hope for patients who have exhuasted traditional treatment options.

4. **Long -term survivorship**:- With the increasing success of the treatment regimens, the focus has shifted to the long-term quality of life for Hodgkin's lymphoma survivors. Monitoring for late effects and complications has become crucial in survivorship care.

5. **Challenges and Future Directions**:- Despite significant progress, challenges persist, including the management of treatment-related toxicities, refractory cases, and the development of resistance to immunotherapies. Ongoing research efforts must address these hurdles and explore novel therapeutic strategies.

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