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CLASSICAL HODGKIN LYMPHOMA: FROM PAST TO FUTURE-A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY AND THERAPEUTIC ADVANCES

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ABSTRACT

Lymphatic system cancers include Hodgkin lymphoma. The immune system's role in warding off sickness and germs consists of the lymphatic system. Hodgkin lymphoma develops when normally functioning lymphatic cells transform and proliferate uncontrollably. The annual incidence of Hodgkin lymphoma is two to three cases per one hundred thousand individuals. Nodular lymphocyte predominance (NLPHL) and classical Hodgkin lymphoma (cHL) are the two subtypes of Hodgkin lymphoma that are distinguished based on immunohistochemically and visual characteristics. Upon first diagnosis, the majority of individuals with Hodgkin's lymphoma will have supradiaphragmatic lymphadenopathy. Inguinal lymph node involvement is infrequent, however, patients commonly report lymph node involvement in the neck, anterior mediastinal, supraclavicular, and axillary areas. Chemotherapy and radiation therapy are the fundamental components of treatment for classical Hodgkin lymphoma (cHL), although in certain instances of slow-growing non-Hodgkin lymphoma, monitoring may be considered a viable approach.

KEYWORDS: *Hodgkin lymphoma, Epstein-Barr virus, Nodular lymphocyte predominance, Immunotherapy, Graft-versus-host disease.*

INTRODUCTION

Approximately 8,540 new cases of Hodgkin lymphoma (HL) are reported annually in the United States. The condition exhibits a bimodal distribution, wherein the frequency of occurrence is higher among individuals aged 55 years and above compared to younger individuals. The cause of HL is currently unidentified, and there are presently no identified risk factors associated with the onset of the disorder. HL has been associated with various risk factors, including viral exposure, a weakened immune system, or genetic vulnerability. Individuals diagnosed with HL have a significantly increased likelihood of transmitting the disease to their siblings of the same gender, which is ten times greater than the general population. Furthermore, the likelihood of a patient developing HL is considerably greater if they have a monozygotic twin compared to their dizygotic twin sister. Research indicates that an atypical immune response to infection may contribute to the development of HL. However, the presence of familial characteristics suggests a possible genetic cause. The presence of the EBV genome was detected in HL tumor samples. Epidemiological and serological research have established a correlation between the Epstein-Barr virus (EBV) and human lung disease (HL). However, several viral illnesses that occur during childhood, such as chickenpox, measles, mumps, rubella, and pertussis, actually decrease the likelihood of getting HL [1]. They may also offer a certain level of security. Moreover, there exists a correlation between HIV infection and hearing loss (HL); the likelihood of experiencing HL is significantly greater in those who are HIV-positive compared to the overall population. Individuals with compromised immune systems, namely those who are afflicted with HIV, experience a less favorable outlook following the initiation of HL treatment. Moreover, at initial detection, the disease typically exhibits advanced progression and may be seen in atypical locations. There has been a substantial rise in the number of patients who have achieved a cure in the past four decades due to tremendous progress in combination chemotherapy, targeted immunotherapy, and radiation therapy. Currently, almost 80% of persons under 60 who have been newly diagnosed have a high likelihood of achieving complete recovery.[2] Age, gender, and geographic location are factors that influence the frequency of Hodgkin lymphoma. Hodgkin lymphoma exhibits a higher prevalence in males, teenagers, and young adults, as well as individuals with a previous Epstein-Barr virus infection, HIV/AIDS, autoimmune disorders, exposure to environmental factors, smoking habits, and a family history of the disease. Furthermore, research demonstrated that variables such as the number of individuals in a family and the socioeconomic condition of individuals had an impact on the occurrence of Hodgkin lymphoma. Before implementing

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targeted preventive measures in individual countries, it is essential to evaluate the worldwide distribution pattern, risk factors, and historical trends of Hodgkin lymphoma. This is necessary because the epidemiology of the illness varies and may have undergone changes over time.[1, 3]

EPIDEMIOLOGY

The annual incidence of Hodgkin lymphoma is approximately 2 to 3 cases per 100,000 individuals. Aside from the primary age peak shown in those aged 30 to 40, there is a secondary peak observed in individuals aged 60 and above. Hodgkin's lymphoma can arise as a result of several advantageous conditions. The remarkably high occurrence of identical twins offers compelling evidence for a significant genetic factor in HL. A limited range of genetic variations in genes that regulate immune system function have been linked to a higher vulnerability to horizontal gene loss. Approximately 45% of persons diagnosed with Hodgkin's lymphoma (HL) have positive results on Epstein-Barr virus (EBV) tests. An attribute of the Epstein-Barr virus subtype, referred to as nodular sclerosing, is the occasional appearance of the internal genome. Ultimately, it appears that in certain individuals, a past Epstein-Barr virus (EBV) infection that has reached its expiration date can initiate the onset of Hodgkin's lymphoma (HL), however, it is not the sole factor contributing to HL. HIV-positive individuals often have a heightened likelihood of acquiring Hodgkin's lymphoma (HL).[4] The introduction of Highly Active Anti-Retroviral Therapy (HAART) has led to an increase in Hodgkin's lymphoma (HL) cases associated with HIV. This increase highlights the importance of the inflammatory environment in enhancing the immune system's ability to fight the disease. An individual's susceptibility to sickness can be influenced by genetic predisposition, exposure to viruses, and lifestyle choices made within specific socioeconomic groups.[5]

Pathophysiology

Neoplastic cells of various types can be found in both the conventional and NLP-HL varieties of Hodgkin lymphoma. Reed-Sternberg (RS) cells, which are large cancer cells, possess two symmetrical nuclei that bear a resemblance to the eyes of an owl. These nuclei are observed in distinction to the surrounding reactive cells. The presence of the Reed-Sternberg cell implies a characteristic instance of Hodgkin's lymphoma. Germinal center B cells harboring mutations in the IgH-variable region segment are employed for the generation of RS cells. Reactive cells secrete cytokines, including interleukin-5 (IL-5) and transforming growth factor-beta (TGF-beta), to attract other cells. An RS cell is typically characterized by aneuploidy and the absence of a persistent cytogenetic abnormality. According to the existing evidence, most of the isolated RS cells exhibited clonal rearrangement of Ig genes. [6] In immunohistochemistry, RS cells exhibit positive staining for CD30 and CD15, but CD20 and CD45 are usually negative. Conversely, Neoplastic NLP-HL cells exclusively display positive staining for CD20 and CD45. RS cells commonly express PAX5, CD25, HLA-DR, ICAM-1, Fascin, CD95 (apo-1/fas), TRAF1, CD40, and CD86, in addition to CD15 and CD30. RS cells encompass several types, such as lacunar, mummified, and Hodgkin cells. Hodgkin cells are the components of mononuclear RS-cell variations. Mummified cells exhibit a contracted cytoplasm and a reddish nucleus with indistinct chromatin. Lacunar cells exhibit nuclei with many lobes, abundant pale cytoplasm, and tiny nucleoli. During tissue fixation and sectioning, the cytoplasm typically undergoes contraction, resulting in the formation of a lacune-like region surrounding the nucleus.[7]

Lymphocytic and histiocytic cells, often known as "popcorn cells" or LP cells, are characterized by their greater size and folded multilobulated nuclei. One distinguishing feature of NLP-HL is the presence of these cells. Conversely, the NLP-HL does not possess the usual RS cells. LP cells exhibit smaller nuclei and more basophilic nucleoli when compared to RS cells. Only isolated single LP cells have clonally altered immunoglobulin genes. LP cells are characterised by the positive expression of C020, CD45, EMA, CD79a, CD75, BCL6, BOB.1, OCT2, and J chains.[8]

B-cell lymphoma arises in the germinal center, which lacks the characteristic features of B-cells. Hypermutated immunoglobulin genes in human RSV cells exhibit chromosomal rearrangements. These genes are non-functional and do not produce the B-cell receptor on the cell surface. In normal circumstances, this would induce apoptosis in B cells. However, in Hodgkin's lymphoma, it seems that other oncogenic pathways have hindered this process.

Aside from ongoing intracellular growth and survival signals, HRS cells also rely on a specific cellular milieu known as the tumor microenvironment (TME). The majority of Hodgkin's lymphoma (HL) lesions consist of Hodgkin and Reed-Sternberg (HRS) cells. However, HRS cells constitute a small proportion of the cells present in malignant tumors. The HL microenvironment consists of tumor-associated macrophages, mast cells, eosinophils, lymphocytes, granulocytes, and fibroblasts. The histological subtype of classical Hodgkin lymphoma (cHL) affects the number of immune cells.[9] The development of innovative therapeutic options for HL has been made possible by the progress in our understanding of its biology. This progress has been achieved by enhancing our understanding of how HRS cells hinder natural killer (NK) and T-cell-mediated antitumoral immune responses.

Genomic examinations of HRS cells have revealed that the changes in the way these cells interact with the inflammatory environment are primarily due to genetic abnormalities. Antigen presentation can be impeded by downregulation, loss-of-function mutations in B2M, or translocations that decrease the quantity of MHC class I or II presentations on the HRS surface due to CIITA. In addition, HRS cells frequently exhibit amplification of genes on chromosome 9p24.1 that encode the ligands PDL1 and PDL2.

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These ligands are receptors involved in programmed cell death. The interaction between PDL1/2 and PD1 is believed to be a crucial process in the development of T-cell exhaustion. The aberrant production of MICA by HRS cells may hinder the antitumoral immune response mediated by NK cells.[10]

The specific mechanisms by which HRS cells interact with their inflammatory environment in diverse ways are still not fully understood. The research conducted using multiplex immunofluorescence and digital image analysis reveals that HRS cells primarily interact with nearby PD1+CD4+ T cells and PDL1+ macrophages, while the presence of CD8+ T cells near HRS cells is infrequent. Mass cytometric analysis has validated that classical Hodgkin lymphoma (cHL) necessitates an immunosuppressive, Th1-polarized setting with a predominance of CD4+T cells.[11]

CLASSIFICATION

Two subtypes of Hodgkin lymphoma can be differentiated based on immunohistochemical and visual characteristics: Nodular lymphocyte predominance (NLPHL) and classical Hodgkin lymphoma (cHL). Although more than 90% of cases are classical Hodgkin lymphoma (cHL), nodular lymphocyte-predominant Hodgkin lymphoma (LPHL) often has a gradual growth pattern but can also behave aggressively, like a tumor. This study focuses on the four histologic subtypes of classical Hodgkin lymphoma (cHL), which are distinguished based on their morphology, the quantity of Hodgkin and Reed-Sternberg (HRS) cells, and the level of background infiltration. Hodgkin Reed-Sternberg (HRS) cells, which are cancerous, have a distinct immunophenotypic profile characterized by the presence of CD15 + and CD30 +, and the absence of CD45 −. These cells can be present in all subtypes of classical Hodgkin lymphoma (cHL).[10,12]

Nodular Sclerosis

Nodular sclerosis classical Hodgkin lymphoma (NSCHL) is characterized by the presence of neoplastic lacunar-type HRS cells surrounded by a band-forming sclerosis inflammatory background. Classical Hodgkin lymphoma is predominantly caused by NSCHL in approximately 70% of cases in wealthy nations. Approximately 80% of cases exhibit mediastinal adenopathy, and nodes larger than 10 cm in diameter affect around 50% of patients. When compared to other forms of cH, NSCHL often has a more favorable prognosis and is less frequently associated with the Epstein-Barr virus.[13]

Mixed Cellularity

Differential cellularity refers to the analysis of the different types of cells present in a sample.
MCCHL accounts for around 20-25% of cHL cases in the United States. This particular subtype is more common among individuals who are HIV-positive and reside in socioeconomically deprived settings. There is an absence of sclerosing fibrosis, and the HRS cells are scattered throughout a diverse range of mixed inflammatory tissue. Around 75% of individuals exhibit Epstein-Barr encoded latent membrane protein 1 (LMP1) and EBV small nuclear RNA transcripts (EBER), a prevalence that is notably higher than that of nodular sclerosing cHL.[14]

Lymphocyte Rich

Approximately 5 percent of cases correspond to classical Hodgkin lymphoma (cHL). Lymphocyte-rich classical Hodgkin lymphoma (LRCHL) contains small lymphocytes and occasional Hodgkin Reed-Sternberg (HRS) cells but lacks neutrophils and eosinophils. The specimens in question display a high degree of cellularity or the existence of nodules. Early-stage illness in individuals is typically characterized by peripheral adenopathy without considerable mediastinal involvement. Therapeutic failure is rare when using modern combination chemotherapy regimens, as they often result in favorable therapeutic outcomes.[15]

Lymphocyte Depleted

Lymphocyte-depleted classical Hodgkin lymphoma (LDCHL), the most uncommon kind of cHL, impacts less than 1% of individuals in affluent countries. Identifying the reactive inflammatory infiltrate in tumor tissues is difficult, even when HRS cells are present. When comparing other subtypes of classical Hodgkin lymphoma (cHL) to HIV infection, the clinical progression is more severe and frequently happens in conjunction with it. [16]

Overall, the outlook for patients with NSCHL is considerably more favorable compared to those with MCCHL or LDCHL. Conversely, individuals diagnosed with LRCHL had the highest likelihood of recovery. Aside from subtyping, there exist alternative grading methods that possess predictive capabilities about outcomes, however, their utilization is infrequent. These strategies take into account the characteristics of the tumor, such as the extent of infiltration by cancerous HRS cells, the presence of eosinophilia, and the depletion of lymphocytes. [17,18]

DIAGNOSIS

The majority of individuals diagnosed with Hodgkin's lymphoma will exhibit supradiaphragmatic lymphadenopathy upon initial diagnosis. While the occurrence of inguinal lymph node involvement is uncommon, patients often experience involvement of the

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neck, anterior mediastinal, supraclavicular, and axillary lymph nodes. Approximately one-third of patients experience systemic symptoms, such as fever, night sweats, and weight loss, whereas a larger number of patients suffer from chronic pruritis. Hodgkin's lymphoma (HL) typically originates in clusters of adjacent lymph nodes, but it can infiltrate or metastasize to organs beyond the lymph nodes via the bloodstream. The lungs, liver, bone marrow, and spleen are the extranodal regions that are most frequently affected. A biopsy is the only definitive test for confirming the existence of HL. Fine needle aspiration and core needle biopsies are insufficient methods for obtaining a correct diagnosis due to their inability to adequately capture the intricate structure of the lymph nodes. Due to the relatively low frequency of cancer cells in Hodgkin's lymphoma (HL), an inadequate biopsy sample may not include malignant cells. To establish the diagnosis, it is necessary to locate the malignant Reed-Sternberg cell, which originates from the B-cells in the follicular core. This cell must be present in the appropriate cellular milieu, which comprises eosinophils, histiocytic cells, and normal reactive lymphocytes.[19] Hemolymphoid tumors (HL) are classified into two primary categories by the World Health Organisation: classical HL, which is the more frequently diagnosed type, and nodular lymphocyte predominance HL, which is the less prevalent form. The term "clinical HL" encompasses a wide range of HL cases, including lymphocyte-rich HL, mixed cellularity, lymphocyte depletion, and nodular sclerosis. Classical Hodgkin lymphoma (HL) and nodular lymphocyte-predominant HL exhibit significant differences in terms of their biology and clinical appearance. Moreover, there is a strong correlation between nodular lymphocyte-predominant Hodgkin lymphoma (HL) and big B-cell lymphoma, characterized by a significant abundance of T cells and histiocytes. The Clinical Advisory Committee of the International Consensus Classification of Mature Lymphoid Neoplasms has recently determined that a new terminology is necessary to accurately characterize this specific type of Hodgkin's Lymphoma. A proposal was made to rename it as "Nodular lymphocyte predominant B-cell lymphoma (NLPBL)". The extent of available evidence for this is currently uncertain.[20, 21]

TREATMENT

Chemotherapy and radiation therapy are the primary therapeutic options for classical Hodgkin lymphoma (cHL). In certain instances of non-Hodgkin lymphoma that progresses slowly, monitoring may be a viable alternative. Before the advent of combination chemotherapy, the survival rate for individuals with this malignant disease was less than 10% after five years. The overall rates of survival have risen due to advancements in radiation and chemotherapy, as well as a deeper comprehension of cancer's biology. The exceptional treatability of classical Hodgkin lymphoma (cHL) results in a highly positive 5-year relative survival rate for patients aged 0 to 19. The survival rate for individuals diagnosed between the ages of 20 and 64 is 96.4%, whereas for those diagnosed at 65 and older, it is 89.8%.[22,23]

Since the early 1900s, radiation therapy has been employed as a treatment for Hodgkin lymphoma, also known as Hodgkin's disease. For a long time, the mechanisms of transmission, as well as the electromagnetic fields and radiation levels necessary to shift from a palliative care approach to a potentially curative one, were not comprehensively understood. Stanford University's creation of the high-energy linear accelerator in the 1950s enabled more exact dosage distribution and the utilization of more accurate fields. Due to the tendency of classical Hodgkin lymphoma (cHL) to spread to nearby lymph node regions, a viable treatment option is radiation therapy targeting the surrounding areas of the tumor. This method has proven beneficial in treating many patients with early-stage cHL and, in some rare instances, advanced-stage cHL. Extended-field radiation encompassed the regions surrounding the diagnosed sites of illness, whereas involved-field radiation specifically focused on the evident disease locations. "Total nodal irradiation" is a term used to describe the combination of two types of radiation fields: the inverted Y field, which focuses on the abdomen and spleen, and the mantle field, which targets the neck, axillae, mediastinum, and hilar regions. Stanford University research indicates that those who underwent full nodal irradiation experienced an 80% reduction in the likelihood of long-term development. However, there remained a possibility of encountering severe adverse consequences due to radiation exposure. In the era of three-dimensional and PET-directed radiotherapy, medical experts devised involved-site and involved-node radiation fields to mitigate the adverse consequences of radiation exposure.[24]

During the preliminary testing, cytotoxic chemotherapy drugs such as cyclophosphamide, mechlorethamine, and chlorambucil showed promising response rates of 50%. Regrettably, none of these adverse effects endured over the extensive duration of chemotherapy treatments. The introduction of procarbazine and vinca alkaloids greatly facilitated the advancement of combination chemotherapy. The Vincent Devita-led research team at the National Cancer Institute coined the acronym MOPP, which stands for "nitrogen mustard [meclorethamine], vincristine, procarbazine, and prednisone," to describe this specific combination of medications. A total of 81% of persons diagnosed with advanced chronic hemoglobin-related lung illness achieved complete remission within six months following the administration of MOPP treatment. Following a period of four years, during which approximately half of the patients who had achieved a complete response to treatment remained disease-free, the treatment approach shifted from ongoing therapy to a planned goal. [25,26]

Remission was experienced by 96% of participants in both groups. vs to extended-field radiation treatment, the MOPP treatment is a more advantageous option for individuals with Stages IB, IIA, IIB, or IIIA cHL because of its lower relapse rate (13% vs. 35%). Patients who underwent MOPP treatment and received radiation had the highest probability of having a healthy and disease-free life for the expected duration of 10 years. [27]

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Treatment of Pediatric cHL

The intensity of treatment for pediatric chronic hemolytic lymphoma (cHL) varies across North America and Europe, depending on the risk category. The classification of patient risk is essentially determined by characteristics such as cancer stage, severity of disease, and the presence of B symptoms. The staging phase has already established distinct risk categories. The treatment outcomes of juvenile Hodgkin lymphoma patients, as assessed by PET scans, are strongly linked to the radiation dosage in the ongoing COG and European Network investigations. [28] The objective of this strategy is to mitigate the detrimental long-term consequences of radiation therapy in youngsters. Both research groups have adopted highly conformal technologies with reduced radiation volumes to precisely target the most vulnerable locations, aiming to enhance outcomes for high-risk patients. After administering reduced radiation doses, patients receive either standard or intensified chemotherapy treatments. Currently, research is underway to investigate the use of immune-modulating drugs as a response to the possible short-term adverse effects of intensified chemotherapy. [29]

Immunotherapy

Combination chemotherapy is effective in curing most patients with classical Hodgkin lymphoma (cHL). However, for individuals with refractory cHL or cHL that relapses immediately after treatment, immunotherapy has significantly enhanced the outlook. The majority of classical Hodgkin lymphoma (CHL) tumors consist of atypical reactive immune cells, such as lymphocytes, plasma cells, and macrophages, rather than the cancer cells known as Hodgkin Reed Sternberg cells. This characteristic renders these cancers exceptionally distinctive. Neoplastic Hodgkin Reed Sternberg (HRS) cells produce a diverse range of cytokines and chemokines to manipulate their environment and elude the immune system. Tumour immune evasion leads to a reduction in T cell function. The signaling pathway referred to as Programmed death-1 (PD-1)-PD-1 ligand (PD-L1) is a potential mechanism that may be implicated. Cancer cells expressing the PD-1 ligand bind to the PD-1 receptor on T lymphocytes, which hinders the activation and proliferation of T lymphocytes.[30]

Malignant Hodgkin and Reed-Sternberg (HRS) cells exhibit significant upregulation of PD-L1 expression, whereas tumor-infiltrating T cells in classical Hodgkin lymphoma (cHL) display substantially increased levels of PD-1 expression. Furthermore, the presence of Epstein-Barr virus (EBV) infection is responsible for the expression of PD-L1 in classical Hodgkin lymphoma (cHL). 56% of individuals diagnosed with classical Hodgkin lymphoma (cHL) exhibit copy gain, 5% exhibit polysomy, and 36% exhibit chromosomal 9p24.1 amplification. These variations improve the creation and combination of PD-1 ligands through the Janus kinase (JAK)-signal transducer and STAT signaling. Given the multitude of factors involved, it is appropriate to focus on the PD-1/PD-L1 immunological checkpoints for therapeutic purposes. [24]

Nivolumab, a PD-1 antibody, produced a positive response in 87% of patients with advanced chronic hemolytic lymphoma who had received substantial prior treatment. Out of these, 17% achieved a total remission. Out of the individuals in this particular group, 78% experienced a recurrence following autologous stem-cell transplantation, and an additional 78% had a relapse after BV treatment. In addition, the effects endured for an extended duration, with 86% of patients remaining alive after 24 weeks. Out of a total of 80 patients with classical Hodgkin lymphoma (cHL) who were treated with nivolumab, 53 of them showed a positive response that could be detected after completing the whole treatment regimen. Nivolumab demonstrated significant efficacy in reducing cHL tumors while exhibiting a favorable tolerance profile. The predominant adverse effects seen included weariness, dermatitis, and infusion-related responses. [31]

An extensive inquiry was carried out to assess the efficacy of pembrolizumab, a PD-1 inhibitor, in adult patients diagnosed with classical Hodgkin lymphoma (cHL) who had previously been treated with brentuximab vedotin (BV), had undergone an average of four systemic treatments before disease relapse, or had undergone an autologous stem cell transplant. Among the patients, 47% gave incomplete responses, whereas 22% supplied comprehensive answers. The predicted median response time was 11.1 months. [29, 30]

Checkpoint inhibition is associated with extra autoimmune side effects, while standard cytotoxic therapy is associated with toxicities such as nausea, vomiting, and hair loss. The bad results can be attributed to either the augmented migration of CD8 T cells into healthy tissues for cytolysis or the excessive synthesis of cytokines by CD4 T-helper cells. The consequences are caused by an overresponse of T cells. The maculopapular rash is the most often occurring type of skin rash that might occur as a result of immune-mediated adverse effects caused by checkpoint inhibition. There have been documented cases of Sweet's syndrome, toxic epidermal necrolysis, Stevens-Johnson syndrome, and other severe reactions. Individuals diagnosed with classical Hodgkin lymphoma (cHL) have limited access to information. However, it has been observed that approximately 5% of lung cancer patients undergoing PD-1 inhibitor treatment-experienced pneumonia. There is evidence linking the use of immune checkpoint inhibition and the two PD-1 blockers mentioned earlier to instances of fulminant myocarditis. Diarrhea, colitis, and endocrine toxicities such as hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis, and adrenal insufficiency have all been associated with the inhibition of immune checkpoints. Discontinuing the use of anti-PD-1 medicine can significantly decrease the occurrence of major immune-related side

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effects in a therapeutic setting. In severe circumstances, the use of steroids and other immunosuppressive therapies may be necessary. [30]

Despite experiencing clinical improvement, imaging data after undergoing checkpoint inhibitor medication may indicate a deterioration of the condition. False progression or immune-mediated "tumor flare" can occur when patients initiate therapy prematurely. To address this issue in the immunomodulatory therapy of lymphoma, a new set of criteria has been created to evaluate treatment response. An example of a criterion is "indeterminate response," which can be employed to categorize lesions until additional imaging definitively categorizes them as either pseudo-progression or genuine disease progression. [31]

Various sources of donors, such as HLA-haploidentical allo-HCT, have been linked to relapse rates above 40%. However, allogeneic hematopoietic stem cell transplantation (allo-HCT) can potentially provide a cure for refractory or relapsing chronic hemolytic lymphoblastic apathy (cHL). Individuals with a history of allogeneic hematopoietic cell transplantation (allo-HCT) were not included in the initial trials of pembrolizumab and nivolumab for classical Hodgkin lymphoma (cHL) due to concerns that inhibiting PD-1 could potentially exacerbate or induce graft versus host disease (GVHD). A retrospective study was conducted in France to evaluate the safety and effectiveness of nivolumab in twenty patients with classical Hodgkin lymphoma (cHL) who experienced a recurrence after undergoing allogeneic hematopoietic stem cell transplantation (allo-HCT). A remarkable 95% of the comments were addressed, with 42% of them being thorough and elaborate. At the one-year follow-up, neither the overall survival rate nor the median survival rate were achieved or determined.[26]

The administration of the medication had to be discontinued following a single infusion due to the occurrence of graft-versus-host disease (GVHD) in six patients, or 30% of the total, who received nivolumab within one week of the initial dosage. Each of these people had a previous occurrence of acute GVHD. Patients with a prior record of chronic GVHD, but not acute GVHD, were not susceptible to nivolumab-induced GVHD. A separate retrospective study conducted in multiple US centers revealed that 77% of patients exhibited a positive response to the usage of PD-1 blocking. Nevertheless, following the initiation of anti-PD-1 medication, a significant proportion of patients (55%) developed treatment-emergent graft-versus-host disease (GVHD), often occurring after receiving 1-2 doses of checkpoint-blocking therapy. Patients who developed GVHD due to nivolumab treatment had a significantly shorter time interval between receiving allo-HCT and starting nivolumab medication. Unlike those who did not experience GVHD, whose median length varied from 7 to 111 months, the patients in this group had a median duration of 8.5 months (ranging from 2 to 19 months). Although patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT) for recurrent classical Hodgkin lymphoma (cHL) may experience positive effects from PD-1 suppression, there is a potential issue of severe and resistant graft-versus-host disease (GVHD) that can occur unexpectedly. Checkpoint inhibition, a treatment method that is limited by the occurrence of graft-versus-host disease (GVHD), maybe a viable alternative to donor lymphocyte infusion for certain patients with recurrent or refractory classical Hodgkin lymphoma after allogeneic hematopoietic stem cell transplantation (allo-HSCT) who require a tumor response. [28]

The safety of allogeneic hematopoietic stem cell transplantation (allo-HCT) for persons who have recently undergone programmed cell death protein 1 (PD-1) blockade therapy is now a topic of discussion and uncertainty. A retrospective analysis was conducted on 38 lymphoma patients from around the world who had received PD-1 inhibitor therapy before undergoing allo-HCT. The study revealed that there was a cumulative incidence of 23% for grade 2-4 acute GVHD at one year, with a higher rate of grade 3-4 acute GVHD. After one year, 41% of patients were diagnosed with persistent GVHD. Patients who received both a PD-1 inhibitor and a monoclonal antibody targeting CTLA-4 experienced a serious case of graft-versus-host disease (GVHD). Unfortunately, one patient succumbed to grade 4 acute GVHD. Seven individuals developed an uncommon noninfectious feverish illness shortly after receiving a transplant, requiring rigorous treatment with steroids. Prior administration of PD-1 blocking treatment in patients has shown that allogeneic hematopoietic stem cell transplantation (allo-HSCT) is possible. This is supported by a 95% confidence interval (CI) of 89% for overall survival after one year and 76% for progression-free survival after one year (pp. 56-87).[34]

Immunotherapy has significant potential for treating chronic HL due to its outstanding safety record, high response rate, and probable long-term success. In recent years, there has been an investigation into the use of immuno-oncologists in innovative combinations with BV and early treatment programs to address the treatment of cHL patients who have experienced relapse or are unresponsive to chemotherapy. [30]

Allogeneic Stem Cell Transplantation

The scarcity of appropriate donors and the heightened rates of severe sickness and death that patients experience in the time directly preceding and following a transplant have historically limited its use. Allogeneic stem cell transplantation (allo-HCT) can effectively treat diseases in the long run by exploiting the "graft vs. lymphoma effect." The outcomes of allo-HCT have significantly improved over the past fifteen years because of advancements in transplant technology. A meta-analysis of research on allogeneic hematopoietic stem cell transplantation (allo-HCT) revealed that among 1850 patients with Hodgkin's lymphoma (HL), 31% saw

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no relapses within three years, while 41-48% achieved overall survival (OS). From the year 2000 onwards, accrual was linked to a 15-25% survival probability without relapse and a decrease of 5-10% in both non-relapse mortality and relapse rates.[31]

CONCLUSION

In conclusion, Hodgkin lymphoma is a complex disease influenced by various factors and characterized by distinct neoplastic cells. Advances in treatment methods, including chemotherapy, radiation therapy, and immunotherapy, have significantly improved the chances of complete recovery for many patients. Allogeneic hematopoietic stem cell transplantation is a potential cure for relapsed or refractory cases, but there is a risk of graft-versus-host disease.

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