Current Immunotherapy Progress in the Hodgkin Lymphoma

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Abstract. Hodgkin lymphoma, a distinctive cancer affecting the lymphatic system, poses challenges in treatment due to its unique characteristics and the limitations of traditional therapies. This essay delves into the potential of immunotherapy to transform the landscape of treatment for Hodgkin lymphoma. Furthermore, the essay analyses case studies to illustrate the efficacy of these approaches. It presents an overview of the underlying principles, as well as specific immunotherapeutic approaches, such as checkpoint inhibitors, monoclonal antibodies, and CAR-T cell therapy, and their mechanisms. Immunotherapy offers a targeted and personalized alternative to conventional chemotherapy and radiation, presenting promising results in clinical trials. Clinicians manage subtleties in immune-related toxicity and response assessment as the field develops. The goal of immunotherapy research in the initial phases of treatment is to increase cure rates while lowering long-term dangers. Ongoing research and advancements, including checkpoint blockade studies, offer hope for refining treatment approaches and optimizing outcomes in Hodgkin lymphoma. This essay emphasizes the significance of immunotherapy in providing effective and less toxic alternatives, heralding a new era in Hodgkin lymphoma treatment.

Keywords: Hodgkin lymphoma; Immunotherapy; Lymphatic system; Checkpoint inhibitors; Monoclonal antibodies.

1. Introduction

Hodgkin lymphoma (HL) is a unique and infrequent form of cancer that impacts the lymphatic system, a component of the immune system. It accounts for about 10% of all lymphomas, which are cancers of the lymphocytes, a type of white blood cell. Although the precise aetiology of Hodgkin lymphoma is unknown, compromised immune systems, Epstein-Barr virus infections in the past, and relatives with a history of the disease are some variables that may raise the risk of getting the disease.

The symptoms of Hodgkin lymphoma are often subtle and nonspecific, such as painless swelling of lymph nodes, fatigue, unexplained weight loss, and persistent fever. These symptoms can be easily overlooked or mistaken for other conditions, but they are vital for early diagnosis and treatment, which can improve the chances of survival and reduce the complications of the disease.

Chemotherapy and radiation therapy are the usual therapies for Hodgkin lymphoma; while they can kill cancer cells, they can also harm healthy cells and have major adverse effects. Moreover, some patients may not respond well to these treatments or may relapse after a period of remission. Consequently, there is a need for Hodgkin lymphoma therapies that are less harmful and more effective. One of the most promising alternatives is immunotherapy, which utilises the body's own immune system to tackle the disease. Immunotherapy represents a new paradigm in cancer treatment, as it can target cancer cells more specifically and spare normal cells. This essay will explain the principles of immunotherapy and explore the different types of immunotherapies that are used or being developed for Hodgkin lymphoma.

2. Background on Hodgkin Lymphoma

One kind of cancer that starts in the lymphatic system is called Hodgkin lymphoma, and it was named after Thomas Hodgkin, who originally described it in 1832. This system, a vital component of the immune system, includes bone marrow, spleen, lymph nodes, and other lymphoid tissues. Large, multinucleated cells known as Reed-Sternberg cells, which normally make up only a tiny portion of the afflicted tissue, are a distinctive feature of Hodgkin lymphoma.

There are two primary classifications for the disease: nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL). Subtypes of classical Hodgkin lymphoma include lymphocyte-rich, lymphocyte-depleted, mixed cellularity, and nodular sclerosis.

HL has traditionally been treated using a combination of radiation therapy and chemotherapy. Chemotherapy, often administered in regimens like ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) in stage 1 and 2, or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) in stage 3 and 4, remains a primary modality for eradicating cancer cells [1,2]. But it also has a number of negative effects, such as exhaustion, nausea, and hair loss. Recurrent cancers, heart issues, and infertility are examples of long-term negative effects, particularly with anthracycline-containing regimens, present additional challenges [3].

Radiation therapy is frequently used in addition to or after chemotherapy. It uses high-energy beams to target cancer cells. While effective, it can lead to side effects like fatigue, skin changes, and a small risk of secondary cancer [4]. Advances in treatment planning aim to minimize exposure to healthy tissues, reducing long-term complications.

High-dose chemotherapy is followed by the patient's own stem cells being reinfused in an autologous stem cell transplant. may be taken into consideration in cases of relapse or refractory disease. However, this approach is not without risks, including infection, organ damage, and complications associated with the transplant process. Eligibility for this intensive therapy varies among patients.

Despite the successes of these conventional treatments, challenges persist, particularly in cases of treatment resistance or relapsed Hodgkin lymphoma. Some patients may experience long-term side effects impacting their quality of life, and the risk of secondary malignancies emphasizes the need for less toxic yet effective therapeutic alternatives.

In response to these challenges, the exploration of novel treatment approaches, such as immunotherapy, has gained momentum. Immunotherapy holds the promise of targeted interventions that may be less toxic than traditional treatments, offering hope for better outcomes and a higher standard of living to individuals suffering from Hodgkin lymphoma.

3. Immunotherapy and its Principles

Immunotherapy is a method of treating cancer by harnessing the body's natural immune system to combat the disease. Immunotherapy stimulates the immune system to identify, attack, and kill cancer cells more successfully than traditional medical interventions including chemotherapy or radiation, which directly target cancer cells. The fundamental principles of immunotherapy involve activating and enhancing the immune response, improving the recognition of cancer cells, and overcoming evasion mechanisms employed by cancer cells. Strategies include checkpoint inhibition, monoclonal antibodies, and cellular therapies like CAR-T cell therapy, all aimed at bolstering the body's natural defences in the cancer treatment.

3.1. The Immune System's Identification and Defence Against Cancer Cells

The ability of the immune system to recognise and eliminate cancer cells is a dynamic, intricate process. Normal cells with genetic mutations are frequently the source of cancer cells, and the immune system has developed defences to recognise and kill these abnormal cells. T cells are an important subset of immune cells. They are able to identify particular antigens on the surface of cancer cells and cause the body to mount an attack. Dendritic cells, another key component, present these antigens to T cells, activating them and initiating a targeted attack on the cancer cells. Additionally, natural killer (NK) cells can directly recognize and destroy cancer cells. The immune system's adaptive nature allows it to develop a memory response, enhancing its ability to mount more effective and targeted responses upon encountering cancer cells again.

3.2. Rationale Behind Using Immunotherapy for Treating Hodgkin Lymphoma:

The rationale for employing immunotherapy in the treatment of HL is grounded in the unique characteristics of the disease and the potential of immunotherapy to address its challenges. HL is typified by the existence of Reed-Sternberg cells, which frequently evade conventional treatments. Immunotherapy provides a viable alternative by enhancing the immune system's ability to identify and target these particular cancer cells. Checkpoint inhibitors, monoclonal antibodies, and cellular therapies like CAR-T cell therapy are tailored to overcome the evasion tactics employed by Hodgkin lymphoma cells. By leveraging the body's natural defence mechanisms, immunotherapy aims to achieve more targeted and durable responses, minimizing side effects and improving long-term outcomes for individuals with Hodgkin lymphoma.

4. Types of Immunotherapy for Hodgkin Lymphoma and Case Studies

4.1. Checkpoint Inhibitors

Checkpoint inhibitors are a pivotal class of immunotherapy that operates by unleashing the full potential of the immune system. To maintain self-tolerance and prevent overactivation, the immune system naturally contains checkpoints such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Cancer cells can take advantage of these checkpoints, making it more challenging for the immune system to recognise and effectively fight them. By obstructing these inhibitory signals, checkpoint inhibitors effectively unblock the immune system.

4.1.1 Nivolumab

Nivolumab works by blocking the PD-1, it acts as a negative controller for T-cell activation and function [5]. The rise in PD-1 expression typically follows cell activation, and this activation creates senescent cells bearing an exhausted phenotype when PD-1 is activated through its ligands. Following this, a subset of cells undergoes apoptosis. PD-L1 and PD-L2 are ligands for this receptor that are expressed across several immune cells. However, some evidence suggests that Reed-Sternberg cells express PD-L1 and PD-L2 notably highly [6]. In cancer, however, malignant cells can exploit this mechanism to evade immune detection. By inhibiting PD-1, nivolumab interferes with this evasion strategy and improves T cells' capacity to recognise and eliminate cancer cells.

Ansell et al.'s study included 23 patients with R/R cHL in a phase I trial to assess nivolumab's effectiveness and safety in the event of a relapse [7]. In this group of 23 patients who were examined, 87% of them reacted positively to the nivolumab treatment, with 17% having a total positive response. The longevity of this therapy was considerable, with a number of patients employing it for up to two years, as permitted under the set protocol. Progression-free survival among the Hodgkin lymphoma subjects in the first stage of the study stood at 86% during the 24th week, while the average survival of all 23 patients was recorded at 91% after one year and 83% after one and a half years. The majority of the patients in the study had received extensive treatment; many of them had also received an autologous stem cell transplant and had previously received brentuximab vedotin treatment. The results suggest that treatment can be continued safely without increased toxicity, and the drug showed effectiveness over an extended period. Moreover, it was concluded that the drug is safe and effective for sustained usage. Furthermore, a small subset of patients who had finished two years of therapy and were then monitored but continued to progress could undergo retreatment. Another more recent research showed that nivolumab is a viable and effective treatment for relapsed/refractory Hodgkin lymphoma (r/rHL) [8]. A remarkable 90% of patients responded to nivolumab therapy overall, with 40% experiencing complete remission after it was stopped. However, 75% of patients had to follow a modified protocol because of financial constraints. The median progression-free survival was discovered to be 13.1 months following a follow-up of 24.3 months; the overall survival was not attained. Notably, no patient stopped taking nivolumab because of adverse effects, highlighting the medication's favourable safety profile. The most frequent side effect noted was hypothyroidism caused by the immune system. According to the study's findings, nivolumab exhibits similar safety and efficacy in real-world settings, despite hampered dosing and administration schedules.

4.1.2 Pembrolizumab (Keytruda)

Pembrolizumab, marketed under the trade name Keytruda, stands as a groundbreaking immunotherapeutic agent designed to empower the immune system in its battle against cancer. Classified as a PD-1 inhibitor, Pembrolizumab has demonstrated remarkable success in various malignancies, including Hodgkin lymphoma. Pembrolizumab operates by blocking the PD-1 pathway. By attaching itself to PD-1 and blocking its interaction with cancer cells, pembrolizumab interferes with this process. This activates the immune system, especially those that exhibit Reed-Sternberg cell presence in Hodgkin lymphoma.

55 patients with relapsed or refractory HL whose disease worsened during or after brentuximab vedotin treatment were included in a study by Armand et al [9]. Each patient who received extensive pretreatment had a failed BV treatment. Intravenous pembrolizumab injections, 10 mg/kg every two weeks. 31 patients were enrolled, seventy-one percent had previously undergone ASCT, and twenty-six percent were deemed ineligible for transplantation due to chemo-resistant disease, indicating a high-risk patient population heavily pretreated with two to fifteen lines of therapy (55% having received five or more prior therapies). Pneumonitis (10%), diarrhoea (16%), nausea (13%), and hypothyroidism (16%) were the most frequent adverse events (AEs). With no grade IV or death reported, five patients experienced grade III toxicity. With 16% of responses being complete (CR) and 48% being partial (PR), the overall response rate was 65%. Seventy percent of responses came in within 24 weeks, which is an encouraging duration.

4.1.3 Ipilimumab (Yervoy)

Ipilimumab, a monoclonal antibody medication sold under the brand name Yervoy, targets CTLA-4, a protein receptor that suppresses immunity, in order to stimulate the immune system. CTLs have the ability to identify and destroy cancer cells, but this destruction is impeded by an inhibitory mechanism. Ipilimumab blocks this inhibitory mechanism, enhancing the body's immune response. In a heavily pretreated patient population, with 33% having previously experienced BV and 67% having undergone s/p ASCT, the combined use of Vedotin Ipilimumab and Brentuximab in a study showed that the observed ORR of 67% and CR rate of 42% indicate a possible improvement in treatment response when compared to monotherapy. Notably, the 1 mg IPI dose elicited more than half of all responses, indicating that the combination of ADC and low doses of immune stimulation could result in very active effects [10].

4.2. Monoclonal Antibodies

Monoclonal antibodies are synthetic compounds created in a lab to resemble the immune system's recognition and targeting of particular molecules on the surface of cells, including cancer cells, known as antigens. The development of monoclonal antibodies involves creating identical copies (or clones) of a single type of immune cell, allowing for the generation of large quantities of antibodies with precise antigen-binding capabilities.

Monoclonal antibodies are designed to bind specifically to antigens that are either overexpressed or only found on the surface of cancer cells. By doing this, they either directly disrupt the cancer cells' ability to proliferate and survive or identify the cancer cells for immune system destruction. Monoclonal antibodies can act through various mechanisms, such as triggering immune responses, blocking signalling pathways essential for cancer cell survival, or delivering toxic substances directly to cancer cells.

4.2.1 Anti-CD30 antibodies

Anti-CD30 monoclonal antibodies are a category of immunotherapeutic drugs aimed at targeting CD30, a protein expressed on the surface of specific cancer cell types, such as Reed-Sternberg and Hodgkin cells involved in Hodgkin lymphoma. CD30 is a cell surface marker associated with lymphomas and is considered a valuable target for immunotherapy due to its selective presence on malignant cells. One notable example of an anti-CD30 antibody is Brentuximab Vedotin (Adcetris).

An antibody-drug conjugate (ADC) called benuximab vedotin (SGN-35) targets the CD30 antigen, which is present in anaplastic large cell lymphoma and Hodgkin lymphoma. The cAC10 chimerized IgG1 monoclonal antibody SGN30 makes up SGN-35. A valine-citrulline dipeptide linker has been added to facilitate the attachment of monomethyl auristatin E (MMAE), a potent inhibitor of microtubule polymerisation. Based on a pivotal phase II study that demonstrated an ORR of 75%, the US Food and Drug Administration approved it in 2011 for the treatment of R/R cHL and ALCL [11].

Another research focus on stage III or IV cHL demonstrated that, among 1334 patients, those receiving 6 cycles of A+AVD showed a 3-year progression-free survival (PFS) rate of 83.1%, surpassing the 76.0% rate with ABVD at a 37-month follow-up. Notably, A+AVD exhibited consistent efficacy across disease stages and risk factors, offering independent benefits. PET2- patients under 60 years of age saw a 3-year PFS of 87.2% with A+AVD and 81.0% with ABVD. A+AVD outperformed ABVD with a 69.2% 3-year PFS rate, even in PET2+ patients under 60 years of age. Furthermore, A+AVD showed resolution or improvement of peripheral neuropathy in 78% of cases, consistent with ABVD results (83%) [12]. These findings highlight the long-term effectiveness of A+AVD in treating stage III/IV cHL, providing consistent advantages without the requirement for treatment intensification or bleomycin exposure.

4.2.2 Anti-CD20 antibodies

A class of immunotherapeutic agents known as anti-CD20 antibodies is made to specifically target the CD20 protein, which is expressed on the surface of B cells, both healthy and cancerous. These antibodies have proven to be particularly effective in treating B-cell malignancies, such as non-Hodgkin lymphomas and certain autoimmune disorders involving B cells. One of the most well-known anti-CD20 antibodies is Rituximab (Rituxan). This monoclonal antibody is chimeric and selectively binds to the CD20 antigen found on the surface of B cells. Once bound, it initiates a series of immunological responses, including antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). B cells that express CD20 are destroyed as a result of these processes. Some research points out that Rituximab can be used in combination with chemotherapy regimens, and enhancing the overall treatment efficacy and improving outcomes for patients with B-cell lymphomas [13].

4.3. CAR-T Cell Therapy

Chimeric Antigen Receptor T-cell therapy is a pioneering form of immunotherapy that boosts the immune system's capacity to identify and remove cancer cells. The treatment entails modifying the patient's T cells to produce chimeric antigen receptors (CARs) on their surface by means of genetic engineering. The first step in the process is to remove T cells from the patient's blood. These cells are then genetically modified to create CARs. These CARs are synthetic receptors that combine elements of T-cell signalling with the antigen-binding domain of an antibody. CAR-T cells are cultivated in a laboratory so that a substantial quantity of them can be produced. The specific antigens on the surface of cancer cells are the target of CAR-T cells. After the desired quantity is achieved, the patient is once again given the modified T cells. CAR-T cells become active when they come into contact with target cells and mount a powerful defence. This activation prompts the release of cytotoxic substances and cytokines, ultimately resulting in the destruction of cancer cells.

CAR-T cell therapy has demonstrated a remarkable clinical response in patients with relapsed or resistant Hodgkin lymphoma, particularly in those who have not responded to standard therapy. Studies on patients receiving CAR-T cell therapy have demonstrated long-lasting remissions and high response rates [14].

The effectiveness of CAR-T cell therapy in treating Hodgkin lymphoma is believed to be related to the targeted expression of CD30, an antigen expressed on the surface of Reed-Sternberg cells, the characteristically malignant cells in the disease. Using a targeted and individualised therapeutic approach, CD30-directed CAR-T cells efficiently locate and eradicate these cancer cells.

5. Comparison with Traditional Treatments

Immunotherapy and traditional treatments for HL present distinctive approaches with varying impacts on efficacy, side effects, and long-term outcomes. Traditional treatments, encompassing chemotherapy and radiation, often induce remission but carry a burden of systemic side effects and potential long-term complications. Immunotherapy, on the other hand, introduces a paradigm shift by leveraging the body's immune system, showing promising efficacy, especially in cases resistant to traditional interventions. While traditional treatments have established long-term survival for many patients, immunotherapy offers the potential for durable responses and reduced late effects. The side effect profiles differ, with traditional treatments affecting rapidly dividing normal cells and immunotherapy triggering immune-related adverse events. Ongoing research explores personalized and combination approaches, aiming to optimize the balance between efficacy and side effects, thus shaping a more tailored and effective treatment landscape for Hodgkin lymphoma [15].

6. Challenges, Future Directions and Research

Immunotherapy, while promising, is not without its challenges. A significant concern pertains to potential side effects that may range from mild to severe and vary according to the type of immunotherapy employed. Immune-related adverse events may affect healthy tissues as the immune system becomes hyperactive.

Resistance to immunotherapy is another significant challenge. Even when cancer cells are initially resistant to therapy, they can develop defences against the immune system. Tumour microenvironment factors, such as the presence of immunosuppressive cells or molecules, can contribute to treatment resistance. Additionally, the heterogeneity of cancer cells within a tumour may result in subsets that are less responsive to immunotherapeutic interventions.

Currently, comprehensive research on the differences between different immunotherapies and how to customise treatments based on particular symptoms is lacking. This gap poses a significant challenge in cancer care. To address this, it's essential to conduct in-depth studies exploring the unique mechanisms, side effects, and efficacy of different immunotherapeutic approaches. To tackle this challenge, ongoing research should focus on identifying biomarkers predicting responses to specific immunotherapies, enabling precise treatment selection. Developing guidelines and algorithms based on individual patient characteristics will empower healthcare professionals to make informed decisions.

Current research in immunotherapy for Hodgkin lymphoma is marked by a focus on refining existing approaches and exploring novel strategies. Research on checkpoint inhibitors is still ongoing, especially those that target PD-1 and PD-L1. In an effort to improve treatment outcomes, researchers are also exploring the use of combination therapies and bispecific antibodies. Furthermore, research is being done to find biomarkers that can predict an immune therapy response, which will help with patient selection and individualised treatment plans.

7. Conclusion

In conclusion, the exploration of immunotherapy in the context of Hodgkin lymphoma unveils a promising frontier in cancer treatment, challenging traditional therapeutic approaches. Throughout this essay, the principles of immunotherapy will be discussed, including checkpoint inhibitors, monoclonal antibodies and the revolutionary CAR T-cell therapy. By utilising the immune system, these cutting-edge tactics provide a focused and individualised method of treating Hodgkin lymphoma. The key points highlighted underscore the success of immunotherapy in various clinical trials, presenting a compelling case for its efficacy and potential to redefine the treatment paradigm for Hodgkin lymphoma. Specifically, checkpoint inhibitors have produced remarkable results by empowering the immune system to recognise and eliminate cancer cells. Monoclonal antibodies, with their targeted precision, and CAR-T cell therapy, with its customized cellular warfare, further contribute to the arsenal against this malignancy.

In transitioning from traditional therapies to immunotherapy for Hodgkin lymphoma, clinicians grapple with nuanced considerations. Follow-up data challenges the conventional emphasis on complete responses, revealing durable outcomes across diverse response categories. Immunotherapy introduces unique response patterns, necessitating a revaluation of assessment criteria; Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) recognizes this atypicality. Managing immune-related toxicities poses distinct challenges, demanding a delicate balance between therapeutic efficacy and safety. As immunotherapy advances into earlier treatment stages, preserving high cure rates becomes paramount. Integrating immunotherapy at earlier stages may mitigate long-term risks, and ongoing studies exploring checkpoint blockade offer promise for refining treatment approaches in Hodgkin lymphoma, fostering optimism for improved outcomes.

References

[1] Diehl, V., Thomas, R. K. & Re, D. Part II: Hodgkin's lymphoma—diagnosis and treatment. The Lancet Oncology 5, 19–26 (2004).

[2] Diehl, V. Dose-escalation study for the treatment of Hodgkin's disease. Annals of Hematology 66, 139–140 (1993).

[3] Schilsky, R. L. et al. Long-term follow-up of ovarian function in women treated with MOPP chemotherapy for Hodgkin's disease. The American Journal of Medicine 71, 552–556 (1981).

[4] Aleman, B. M. P. et al. Long-Term Cause-Specific Mortality of Patients Treated for Hodgkin's Disease. Journal of Clinical Oncology 21, 3431–3439 (2003).

[5] Zou, W., Wolchok, J. D. & Chen, L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. Science Translational Medicine 8, (2016).

[6] Roemer, M. G. et al. PD-L1 and PD-L2 Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome. Blood 126, 176–176 (2015).

[7] Ansell, S. M. et al. PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma. New England Journal of Medicine 372, 311–319 (2015).

[8] Pathak, N. et al. Modified Protocol of Nivolumab in Relapsed/Refractory Hodgkin Lymphoma: A Brief Communication of Real-World Data. Journal of Immunotherapy 45, 239–242 (2022).

[9] Armand, P. et al. Programmed Death-1 Blockade with Pembrolizumab in Patients with Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure. Journal of Clinical Oncology 34, 3733–3739 (2016).

[10] Diefenbach, C. S. et al. Preliminary Safety and Efficacy of the Combination of Brentuximab Vedotin and Ipilimumab in Relapsed/Refractory Hodgkin Lymphoma: A Trial of the ECOG-ACRIN Cancer Research Group (E4412). Blood 126, 585–585 (2015).

[11] Younes, A. et al. Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients with Relapsed or Refractory Hodgkin's Lymphoma. Journal of Clinical Oncology 30, 2183–2189 (2012).

[12] Straus, D. J. et al. Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study. Blood 135, 735–742 (2020).

[13] Kasamon, Y. L. et al. Phase 2 study of rituximab-ABVD in classical Hodgkin lymphoma. Blood 119, 4129–4132 (2012).

[14] Ramos, C. A. et al. Anti-CD30 CAR-T Cell Therapy in Relapsed and Refractory Hodgkin Lymphoma. Journal of Clinical Oncology 38, 3794–3804 (2020).

[15] Bair, S. M., Mato, A. & Svoboda, J. Immunotherapy for the Treatment of Hodgkin Lymphoma: An Evolving Paradigm. Clinical Lymphoma Myeloma and Leukemia 18, 380–391 (2018).