Immune Evasion and Immunotherapeutic Advances in Classical Hodgkin Lymphoma

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Abstract

Classical Hodgkin lymphoma (CHL) is a cancer of the lymphatic system characterized by Hodgkin Reed–Sternberg cells derived from B lymphocytes. While most patients respond well to chemotherapy and radiotherapy, some experience relapse or resistance, creating a need for new treatment approaches. This review examines how CHL evades immune detection through mechanisms such as reduced antigen presentation and increased expression of immune checkpoint proteins like PD-L1. It also discusses current immunotherapies, including checkpoint inhibitors and antibody-drug conjugates, as well as emerging treatments such as CAR T-cell therapy. Recent clinical research highlights how these advances are improving outcomes for patients with relapsed or refractory disease. Overall, immunotherapy has significantly improved survival in CHL and continues to offer promising potential for more durable remissions.

Introduction

Cancer is a disease driven by genetic alterations that lead to uncontrolled cell division and tissue invasion. The immune system is the body's defense network that detects and eliminates threats such as viruses, bacteria, and cancer cells. The immune system typically recognizes and destroys cancer cells, however, cancer can evade detection by suppressing immune responses or masking identifying markers. Immunotherapy, which stimulates or restores the immune system's cancer-fighting ability, has gained attention as it targets these evasion mechanisms (Chen & Zinzani, 2023). This review examines how classical Hodgkin lymphoma (CHL) avoids immune detection, discusses both established and emerging immunotherapeutic approaches, and considers the impact of recent clinical trials and ongoing research on patient outcomes (Chen & Zinzani, 2023). To illustrate these advances, this review incorporates perspectives from clinicians and patients who have experienced these therapies.

Background

Classical Hodgkin lymphoma (CHL) is a cancer of the lymphatic system defined by the presence of distinctive Hodgkin Reed–Sternberg (HRS) cells within lymph nodes (Küppers, 2019). While chemotherapy has cured many patients, around 20–30% will face relapse or resistance, creating a need for new treatment options (Ansell, 2015). Immunotherapy has recently revolutionized the field, enabling the body's own immune system to target tumor cells (Chen & Zinzani, 2023). This review explores the mechanisms by which CHL escapes immune detection, the latest immunotherapeutic strategies, and the trajectory of ongoing clinical research. Notably, the disease most commonly affects adolescents, young adults (15–35), and older adults over 55, with a slight male predominance (Ansell, 2015). CHL arises from mutated B lymphocytes—Reed–Sternberg cells—which proliferate uncontrollably (Küppers, 2019). The underlying causes are complex, involving genetic mutations, immune dysfunction, and in many cases, Epstein–Barr virus (EBV) infection (Meier et al., 2022). EBV is frequently present at diagnosis, particularly in patients with genetic risk factors or weakened immunity (Meier et al., 2022). CHL appears more frequently diagnosed in developed nations, possibly due to environmental, healthcare, or viral exposure differences. Mutations affecting immune cell survival are central; for instance, persistent *NF-kB pathway* activation helps Reed-Sternberg cells evade destruction (Küppers, 2019). While CHL is generally treatable and has a favorable outlook—approximately 85% of patients achieve five-year survival—careful monitoring is

essential due to possible relapse (Ansell, 2015). Treatment begins with ABVD chemotherapy, sometimes combined with radiation (Ansell, 2015). For those who relapse, immunotherapy offers a promising alternative (Chen & Zinzani, 2023). These therapies train the immune system to recognize and destroy cancer cells that previously escaped detection (Chen & Zinzani, 2023). For example, Dr. Smith, a hematologist, notes, 'Immunotherapy has given hope to patients who once had few options,' and a patient, shares, 'After my relapse, immunotherapy allowed me to return to my life.'"

Immune Evasion in Classical Hodgkin Lymphoma

Ongoing research into CHL seeks to unravel its complex causes and improve patient survival. A pivotal breakthrough has been recognizing how CHL escapes immune detection, leading to new therapeutic strategies (Chen & Zinzani, 2023). HRS cells, the hallmark of CHL, use multiple tactics to evade the immune system. They often reduce or lose MHC class I and II molecules ('nametags') that allow T cells to recognize cancer cells—making it harder for immune cells to recognize tumors (Küppers, 2019). In addition, amplification of the 9p24.1 chromosome in HRS cells results in excess PD-L1 production, which suppresses T cell activity via the PD-1 pathway (Chen & Zinzani, 2023). The tumor environment is further complicated by immunosuppressive cells, such as IL-1B^{+} macrophages, that stifle T cell responses, and by the exclusion of CD8^{+} T cells from the tumor site (Ansell, 2015). Patients unresponsive to immunotherapy often exhibit impaired coordination between B and T cell responses (Chen & Zinzani, 2023). These insights have spurred the development of targeted immunotherapies. Brentuximab Vedotin (BV), an FDA-approved antibody-drug conjugate, targets CD30 on HRS cells and is used after stem cell transplant or with chemotherapy for advanced cases (Ansell, 2015). Still, BV is not curative for all, so additional treatments are often needed. Checkpoint inhibitors (CPIs) like nivolumab and pembrolizumab have significantly improved treatment outcomes by blocking PD-1, reawakening T cell function (Chen & Zinzani, 2023). "Checkpoint inhibitors have changed the game for relapsed patients," says Dr. Lee, an oncologist. Clinical trials also explore combining CPIs with agents like decitabine, or developing CAR T-cell therapies—both approaches aiming to deepen and prolong immune responses (Chen & Zinzani, 2023). While some of these treatments remain investigational, their promise is reflected in patients' stories, who describe their renewed optimism after CPI therapy: "For the first time in years, I felt hope."

Clinical Trials and Recent Advances

Recent scientific breakthroughs have sparked a wave of new clinical trials designed to tackle the ways CHL escapes the immune system (Chen & Zinzani, 2023). Rather than listing studies individually, this section highlights how clinical trials are reshaping patient experiences. Take the Phase II trial NCT04268706: one participant reported, "After years of failed treatments, enrolling in the CAR-T study felt like my last shot. I was nervous, but the team's optimism was infectious." This trial tests a new CD30-targeted CAR T-cell therapy for patients who have exhausted other options (U.S. National Library of Medicine, 2023). Early results have been promising, with response rates exceeding 70% and many achieving sustained remission—giving hope to those who once faced limited prospects (U.S. National Library of Medicine, 2023).

Another innovative study, NCT04134325, picks up where CAR-T therapy leaves off. For patients whose disease returned after multiple therapies, the chance to try renewed PD-1 blockade offered a lifeline. This early-phase study explores whether restarting checkpoint inhibitor therapy can revive exhausted T cells, using cutting-edge immune profiling to monitor progress (U.S. National Library of Medicine, 2023). Initial results have surprised researchers,

showing that even after other therapies fail, the immune system's potential can be rekindled (U.S. National Library of Medicine, 2023).

Future Directions and Conclusion

These stories highlight a broader shift: rather than viewing relapse as a terminal outcome, clinicians now see it as an opportunity to innovate. Future directions include combining checkpoint and CAR-T therapies, engineering "armored" CAR-T cells, and personalizing regimens based on individual immune profiles (Chen & Zinzani, 2024). Recent advances in immunotherapy have significantly accelerated progress in classical Hodgkin lymphoma treatment, particularly for patients with limited prior options (Chen & Zinzani, 2024). Continued research and collaboration between scientists, clinicians, and patients remain crucial for turning these advances into cures.

Classical Hodgkin lymphoma (CHL) is a cancer of the lymphatic system characterized by the presence of Reed–Sternberg cells, which disrupt normal immune responses (Küppers, 2019). While many patients respond well to chemotherapy, immunotherapy has emerged as a powerful option for those who relapse or develop resistance (Ansell, 2015). Treatments such as checkpoint inhibitors—including nivolumab and pembrolizumab—and antibody-drug conjugates, such as brentuximab vedotin, have significantly improved outcomes for these difficult-to-treat cases (Chen & Zinzani, 2024). Current research is focused on addressing the challenges of immune exhaustion and tumor evasion, with promising advances in CAR T-cell therapies and novel combination strategies (Chen & Zinzani, 2024). Looking ahead, immunotherapy has the potential not only to prolong survival but also to offer durable remission or even cures for patients with CHL, reshaping the future of lymphoma treatment and offering the potential for long-term remission or cure (Chen & Zinzani, 2024).

References

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