Chapter 3
Immunotherapy in Hodgkin Lymphoma and Other CD30+ Lymphomas

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Hodgkin Lymphoma

Background/Epidemiology

Hodgkin lymphoma (HL) is an uncommon, B-lymphocyte-derived malignancy, comprising about 11% of all lymphomas seen in the United States and 0.5% of all new cancer cases in the United States. It has an approximate annual incidence of 2.6 new cases per 100,000 men and women per year, with an estimated 8260 new cases occurring in 2017 across the United States [3]. HL is traditionally associated with a bimodal distribution of occurrence, with a median age at diagnosis of 39 years [3]. Siblings of HL patients seem to have an increased risk of developing the disease. Interestingly, siblings of the same gender have been shown to be at twice the risk of siblings of the opposite gender [4]. Studies suggest a possible predilection between ethnicity, socioeconomic status, and HL incidence. Certain HL histologic subtypes like mixed cellularity and lymphocyte-depleted occur more in patients of Hispanic origin with lower socioeconomic status, while another subtype, nodular sclerosis HL, happens more frequently in patients with higher socioeconomic standard of living [5].

Histopathology/Pathogenesis

Based on differences in the histology and phenotype of the tumor cells, HL is divided into two discrete disease entities: classical HL and nodular lymphocyte-predominant

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HL [6]. Classical HL (cHL) is further split into four subsets: nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted. While there are minor variations between the cHL subtypes in clinical presentation, the overall prognosis and treatment for these subtypes are similar. On the other hand, nodular lymphocyte-predominant HL (NLPHL) is distinct in immunophenotypic and genomic features, presentation, prognosis, and treatment. Importantly, it is usually negative for CD30, but positive for CD20 and is treated in a fashion analogous to indolent non-Hodgkin lymphomas. Since it lacks the CD30 antigen, NLPHL will not be included in this discussion.

The characteristic pathologic feature of cHL is the presence of Reed-Sternberg (RS) cells, which are large, multinucleated cells present within a dense, reactive cellular environment made of granulocytes, lymphocytes, dendritic cells, and monocytes. The actual occurrence of RS cells within the cellular background is quite rare, another hallmark of cHL, generally comprising just 1–2% of the cell population [7]. Although RS cells definitively express CD30, they possess an atypical immunophenotype capable of mixed co-expression of myeloid, granulocytic, T cell, and B cell markers [8]. As is the case with most hematologic malignancies, the disease cause is likely multifactorial. RS cells originate from mature germinal center B cells, based on studies showing these cells carrying clonal and somatically mutated immunoglobulin heavy- and light-chain gene rearrangements [9]. However, they have a universal paucity of B cell gene expression, by specifically downregulating expression of B cell transcription factors which causes loss of B cell receptor (BCR) expression on the surface [10]. Normally, the loss of BCR surface expression would shunt a B cell to rapid apoptosis, which indicates that RS cell precursors acquire additional pathogenetic steps that allow for escape from this fate.

Interestingly, in 40–50% of cHL, the RS cells are latently infected with Epstein-Barr virus (EBV) [11]. Since the RS cells are clonally infected, it raises the possibility that EBV infection can be an early and critical step for cHL formation [12]. The RS cells express the EBV-encoded antigens EBNA1, LMP1, and LMP2a, which are weakly immunogenic but may confer a survival benefit on RS cells by mimicking the CD40 receptor and BCR stimulatory signaling [13, 14]. RS cells also show genomic gains of genes that specifically result in dysregulated and constitutive activity of the transcription factor NF-κB and JAK/STAT pathways [15–18]. Genes for TNFAIP3 and SOCS1 that negatively regulate these same pathways are often found to be mutated or inactivated which further promote proliferation and survival of malignant cells [19, 20].

cHL also dictates the composition of its tumor microenvironment by selectively recruiting cells that support cHL survival through either cell-cell interactions or by inhibiting immune antitumor activity, the latter of which is a mechanism also employed by many solid tumor malignancies [21, 22]. RS cells produce chemokines such as MDC/CCL122, IL-10, and TARC/CCL17, which attract regulatory T cells (Tregs) and helper T cells (Th2); these cells then suppress and impair the activity of the few cytotoxic T lymphocytes that gain access to the tumor site [23, 24]. RS cells also overexpress PD-L1 due to gains in chromosomal region 9p24, which further suppresses antitumor activity [25]. This aspect of cHL biology will be addressed further

in the section on therapies for this disease since it results in susceptibility of the tumor cells to checkpoint inhibitors such as nivolumab and pembrolizumab [26–30].

Clinical Presentation

The majority of cHL patients present with palpable but painless supradiaphragmatic lymphadenopathy, commonly in the cervical, axillary, supraclavicular, and mediastinal regions. Subdiaphragmatic lymphadenopathy, bone marrow involvement with resultant cytopenias, splenic involvement, and extra-nodal disease are less frequent presentations. About 35% of cases present with constitutional "B" symptoms, which include fevers/chills, drenching night sweats, and unintentional weight loss of greater than 10% in the preceding 6 months. Other possible systemic symptoms include early satiety, fatigue, shortness of breath, persistent cough, generalized pruritus (often severe and precedes lymphadenopathy), and pain upon alcohol ingestion [31]. These symptoms tend to more commonly occur in patients with bulky or extra-nodal involvement in the spleen, liver, bone marrow, lungs, or a combination of these regions.

Staging/Workup and Diagnosis

Initial workup consists of a comprehensive physical exam and detailed history of symptoms. The physical exam should focus on identifying palpable lymphadenopathy in the cervical, supraclavicular, axillary, inguinal, and popliteal areas. Examination for the presence of hepatomegaly or splenomegaly should also be a focus of the exam. Typical laboratory workup includes a complete blood count with differential, basic metabolic panel, liver function tests, erythrocyte sedimentation rate (ESR), lactate dehydrogenase, and viral studies checking for HIV and hepatitis B. Glucose-6-phosphate dehydrogenase and tumor lysis syndrome (TLS) tests can also be done, but generally cHL does not present with TLS. PET-CT is the standard for imaging cHL due to its improved accuracy compared to CT scans for staging nodal and extra-nodal sites and has replaced the need for bone marrow biopsy to evaluate for marrow involvement [32, 33]. Patients are staged using the modified Ann Arbor staging system [34].

A definitive diagnosis relies upon procuring a full excisional lymph node biopsy for pathology review, since fine needle aspirates and core needle biopsies often do not provide enough tissue sample for an accurate diagnosis. The predominant immunophenotype of cHL RS cells is CD15+, CD30+, MUM1+, CD19−, and CD45−. CD20 can be weakly positive in some RS cells but is generally considered to be negative in cHL.

Additional treatment-related workup includes an echocardiogram to assess a patient's cardiac ejection fraction prior to anthracycline therapy. Pulmonary func-

tion testing with a measurement of the diffusion capacity of the lung for carbon monoxide (DLCO) is required prior to bleomycin treatment. Fertility preservation is typically discussed with patients, although most patients treated with standard frontline therapy regain fertility.

Prognosis

cHL patients are generally sorted into three primary prognostic risk groups: early favorable risk (stages I–II with no unfavorable factors), early unfavorable risk (stages I–II having any one of the unfavorable factors), and advanced stage [35]. The determining prognostic risk factors for early-stage disease are elevated ESR, involvement of >3 lymph node regions, B symptoms, and extra-nodal presentation [36]. The NCCN further delineates the early unfavorable risk group into those with and without bulky disease [37]. The International Prognostic Score identifies several predictive disease factors that project freedom from progression (FFP) and overall survival (OS) in patients with advanced disease. These features include age >45 years, albumin <4 g/dL, hemoglobin <10.5, male gender, stage IV disease, white blood cell count >15,000/μL, and lymphocyte count <600/μL [38]. The more cumulative features a cHL patient has, the worse the prognostic outcome overall for the patient [35–38].

Interim PET-CT (iPET-CT) represents a critical element for prognosticating a patient's overall course and progression-free survival (PFS), with studies showing that it supersedes a patient's IPS score [39]. A negative iPET after two cycles of chemotherapy with ABVD portends a significantly greater PFS than a positive iPET regardless of the disease stage, IPS score, or risk group stratification [39, 40].

Treatment

Standard of care for early-stage HL differs from advanced stage HL. Combination chemotherapy has not changed greatly since the early 1970s in the United States, with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) being the most commonly used regimen [41]. The German Hodgkin Lymphoma Study Group devised a different, more intensive approach consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, or BEACOPP, with standard and escalated variants [42]. BEACOPP is more toxic than ABVD and is not given to patients older than 65 years of age [43]. It also has an increased risk for MDS/AML, treatment-related deaths, and a much higher infertility rate [44, 45].

Treatment for HL can result in secondary malignancies in the breast, lung, and GI tract primarily from the use of radiation therapy [46]. Cardiovascular risk with diastolic dysfunction, myocardial infarction, and cerebrovascular risk can also

occur after receiving XRT to the mediastinum or neck [46]. However, there has been incremental improvement in long-term survival among HL patients due to ongoing modifying of treatment regimens to limit long-term toxicities, especially in early-stage HL [47]. The NCCN favors a risk-based approach for early-stage HL divided into three categories: early favorable, early unfavorable non-bulky disease, and early unfavorable bulky disease. The standard approach for early favorable risk is ABVD × 2 cycles followed by 20 Gy of involved site radiotherapy (ISRT) or ABVD alone × 4 cycles to minimize XRT exposure if mediastinal disease is present [48, 49]. Early unfavorable non-bulky disease can be treated with ABVD × 4 cycles plus 30 Gy of ISRT or ABVD alone × 6 cycles especially if mediastinal disease is present [49, 50]. Early unfavorable bulky disease has a similar approach, although these patients are often treated as advanced stage disease.

For advanced stage cHL (stages III–IV), treatment is primarily with ABVD, with an iPET after cycle 2 determining modulation or intensification of further therapy. Studies have investigated treatment with ABVD versus BEACOPP in advanced stage HL. BEACOPP tended to show improved FFP over ABVD, but at the expense of increased hematologic and non-hematologic toxicities along with the aforementioned higher rates of MDS/AML, infertility, and intolerability in patients above age 65 [51]. Importantly, there was no difference in OS between the two groups. There was a slightly higher proportion of patients with relapsed/refractory disease treated with frontline ABVD compared to BEACOPP, but salvage therapy nullified possible FFP and OS differences between the two treatment groups [51]. In subset analyses of high-risk advanced stage cHL patients, defined as having an IPS score of 3 or greater, there was equivalent EFS and OS between ABVD- and BEACOPP-treated patients [52]. As such, the standard treatment for advanced stage HL in the United States has remained ABVD × 6 cycles. The role of PET-CT-adapted therapy has recently redefined treatment methodologies in advanced stage cHL. If the iPET is negative (defined as Deauville 1–3) after two cycles of ABVD, then bleomycin can be stopped, and the remaining four cycles can be completed with just AVD [53]. This treatment approach is now supported by the NCCN guidelines and would reduce potential pulmonary toxicity from bleomycin. Escalating therapy in patients with a positive iPET from ABVD to eBEACOPP is an option, but has not been evaluated in a randomized fashion [40].

About 15% of patients have primary refractory disease, and additional 15–25% have relapse after an initial complete response. In these patients, the standard treatment is high-dose salvage chemotherapy with subsequent autologous stem cell transplant (auto-SCT). Common salvage regimens include ifosfamide with etoposide and carboplatin (ICE), dexamethasone with cytarabine and cisplatin (DHAP), or gemcitabine-containing regimens (GDP, GVD, BeGEV) [54–58]. Trials comparing salvage chemotherapy with and without auto-SCT showed better disease-free survival with patients receiving auto-SCT [59, 60]. Pre-transplant PET-CT is highly predictive of the outcome with auto-SCT, as patients with a negative pre-transplant PET-CT had a vastly superior EFS compared to patients who had a positive PET prior to auto-SCT [61]. Allogeneic stem cell transplant can be offered as a third-line option if a patient fails auto-SCT.

Anaplastic Large Cell Lymphoma and Other CD30-Expressing Lymphomas

Anaplastic large cell lymphoma (ALCL) is a rare form of NHL, accounting for 3% of all NHLs, and is a subtype of peripheral T cell lymphoma. There are four variants: primary systemic ALCL which is positive for anaplastic lymphoma kinase (ALK) gene rearrangement, ALK-negative primary systemic ALCL, primary cutaneous, and breast-implant-associated. Systemic ALCL has a worse prognosis than the cutaneous or breast-implant-associated subtypes [62]. It has a similar bimodal age of incidence as cHL, but is a disease that occurs more often in the preteen or adolescent age groups [63]. The systemic variants generally have an aggressive presentation with rapidly progressive lymphadenopathy and systemic B symptoms. ALCL has strong CD30 expression, no expression of B cell antigens, and the majority expressing one or more T cell-associated antigens (CD3, CD43, CD45RO). In contrast to HL, they are predominantly negative for CD15 expression. Staging and workup of systemic ALCL is similar to the workup for other aggressive lymphomas with blood work, PET-CT, and excisional biopsy required for definitive diagnosis of systemic disease. Primary systemic ALK-positive ALCL patients have a better prognosis than ALK-negative ALCL patients [64, 65]. Additional prognostic indications include the patient's age at diagnosis, beta-2 microglobulin, and the IPI score [66]. Treatment is usually six cycles of an anthracycline-based regimen such as CHOP, CHOEP, or ACBVP, with patients above age 60 primarily receiving CHOP while those below age 60 receiving the more aggressive treatment regimens [66–68].

In addition to HL and ALCL, various other lymphomas have variable positive expression of CD30. DLBCL can have CD30 expression in approximately 20–25% of cases, while T cell and NK/T cell lymphomas can express CD30 close to 60% of the time [69, 70].

Brentuximab Vedotin

Brentuximab vedotin is a CD30-targeting antibody-drug conjugate linking an anti-CD30 monoclonal antibody with the anti-microtubule agent monomethyl auristatin E (MMAE). Initial studies with the naked CD30 antibody only yielded mediocre results, which led to the conjugation of the antibody to MMAE [71]. In the first phase I trial with brentuximab vedotin (BV), 45 patients with relapsed/refractory CD30+ lymphoma were administered varying doses of the drug to find the maximum tolerated dose (MTD), which was eventually determined to be 1.8 mg/kg intravenously (IV). Out of 12 patients who received the 1.8 mg/kg dose, 6 (50%) achieved an objective response with 4 complete responses (CRs) and 2 partial responses (PRs) [72]. Thirty-six out of forty-two evaluable patients (86%) had discernible tumor regression. The most common adverse events seen were fatigue, pyrexia, diarrhea, nausea, and neutropenia. These results led to a pivotal phase II trial, which had 102 patients with relapsed or refractory HL unresponsive to auto-SCT receiving BV 1.8 mg/kg IV

every 3 weeks for up to 16 cycles [73]. The overall response rate (ORR) was 75%, with 34% of all patients achieving CR. In those patients with an objective response, the median duration of response was 6.7 months; it was 20.5 months in patients reaching CR. Median PFS and OS were 9.3 and 40.5 months in all patients, respectively, and 21.7 months and not reached, respectively, in the CR patients. In long-term follow-up, 13 out of the 34 patients who originally achieved CR (38%) remained in CR [74]. The phase III AETHERA trial looked at 329 relapsed/refractory HL patients with high risk features (defined as refractory to frontline therapy, relapse < 12 months after frontline therapy, or relapse greater than or equal to 12 months with extranodal disease) being apportioned to receive, after auto-SCT, either placebo or up to 16 cycles of BV to assess whether BV could improve PFS when given as consolidative therapy. The median PFS in the BV arm was 42.9 months compared to 24.1 in the placebo arm, leading to BV being approved for treatment of HL patients who had failed at least two prior chemotherapy regimens or auto-SCT, and for use as consolidative therapy in HL patients with high risk features [75, 76].

A multicenter, single-arm, phase I–II trial looked at combining BV with bendamustine, with the hopes of establishing the combination as a possible alternative salvage regimen before proceeding to auto-SCT in relapsed/refractory HL and ALCL patients [77]. Overall, 32% of the patients across both phase I and II achieved a CR. The most serious adverse effects were grade 3 lung infection in 14% of patients in the phase II, and 25% of patients across phases I and II had grade 3–4 neutropenia, with no treatment-related deaths in the study. A second phase I–II study also similarly looked at salvage BV-bendamustine treatment prior to auto-SCT and demonstrated ORR of 92.5% and CR of 73.6% out of 55 evaluable patients [78]. Based on these two clinical trials, the combination of bendamustine with BV appears to be an effective alternative to standard salvage chemotherapy regimens.

BV as first-line treatment in Hodgkin lymphoma has been evaluated. In an early phase I study comparing BV in combination with standard ABVD or combined with a modified standard AVD, a very high rate of pulmonary toxicity was detected in the BV plus ABVD arm [79]. This was not seen in the BV plus AVD arm, so subsequent studies focused on this particular combination. A randomized phase III trial, ECHELON-1, compared first-line BV in combination with AVD against ABVD in patients with stage III or IV cHL [80]. The BV plus AVD arm showed similar efficacy to ABVD and was deemed to demonstrate superior risk reduction in progression, death, and need for additional anticancer therapy compared to the ABVD arm. However, there was a substantial proportion of patients in the BV plus AVD arm who developed peripheral neuropathy (67%), with 31% of patients having grade 2 or higher neuropathy. While the neuropathy was reported to be largely reversible, longer follow-up data is needed to fully study the issue. There were also discrepancies with the mortality and hospitalization rates of patients in the ABVD arm, as they were higher than historical rates with ABVD treatment. Due to these issues, we feel that BV + AVD should not replace ABVD for frontline treatment of Hodgkin lymphoma. However, this remains an excellent option for patients who cannot receive bleomycin due to pre-existing pulmonary disease or abnormal pulmonary function tests.

A recent phase I study investigated the frontline use of BV in combination with cyclophosphamide, doxorubicin, and prednisone (BV-CHP), followed by up to

ten cycles of consolidative BV monotherapy in patients with CD30+ peripheral T cell lymphomas (PTCL). Twenty-six patients were evaluated overall, with 19 having systemic ALCL. One hundred percent of the patients demonstrated an objective response, with a CR of 92% and no patient receiving consolidative stem cell transplant [81]. After 60 months, median PFS and OS were not reached, with estimated 5-year PFS and OS being 52% and 80%, respectively. The primary adverse effect observed was peripheral neuropathy, which resolved or improved in 95% of patients. Based on these results, BV-CHP was evaluated in a phase III trial in CD30-positive PTCL, with CHOP as the comparator arm [82]. This study randomized 226 patients to each regimen, and the results favored BV-CHP in both PFS (median, 48.2 months vs 20.8 months; $p = 0.011$) and OS (median not reached in either group, but there was a 34% reduction in risk of death for BV-CHP; $p = 0.0244$). BV-CHP was FDA approved for frontline treatment of CD30+ PTCL in 2018.

Chimeric Antigen Receptor T Cell Therapy Targeting CD30

Chimeric antigen receptor T cells (CAR-T) are a type of adoptive cellular immunotherapy where a patient's own T cells are genetically reengineered to kill cancer cells by recognizing specific tumor-associated antigens. The chimeric antigen receptor (CAR) itself is a protein construct consisting of an antigen-binding single-chain variable fragment (scFv) derived from a monoclonal antibody, fused via a hinge and transmembrane regions to an intracellular portion containing activation and co-stimulatory domains [83]. The majority of CAR endodomains are comprised of a CD3ζ activation subunit originating from the T cell receptor (TCR) along with a co-stimulatory CD28 or 41BB domain derived from T cell co-stimulatory receptors [83–85]. Initially, the first iterations of CAR-T only possessed the CD3ζ domain. These first-generation CAR-T showed disappointing results in early clinical trials secondary to minimal persistence in vivo, which was thought to be due to lack of a co-stimulatory signal [86, 87]. Physiologically, if normal T cells come across an antigen recognized by their TCR but have no co-stimulatory signal provided from CD80 or CD86, the T cells become anergic and stop proliferating [83, 88]. Due to these clinical findings, the second and subsequent generations of CAR-T have had co-stimulatory endodomains incorporated along with the CD3ζ chain, which have significantly enhanced in vivo proliferation and persistence, and also increased their clinical efficacy [89–91] (Fig. 3.1).

The gene encoding the full CAR construct is transferred into normal patient-derived autologous T cells ex vivo usually via a replication-incompetent retroviral or lentiviral vector, where the CAR gene is incorporated into the T cell genome [88, 92]. These newly transduced CAR-T cells are then grown and expanded in culture ex vivo for 2–4 weeks before being reintroduced back into the patient. Prior to reintroduction, the patient receives a lymphodepleting conditioning chemotherapy regimen to reduce the presence of inhibitory regulatory T cells as well as decrease other cellular elements competing for cytokines [93]. Overall, CAR-T cells combine the

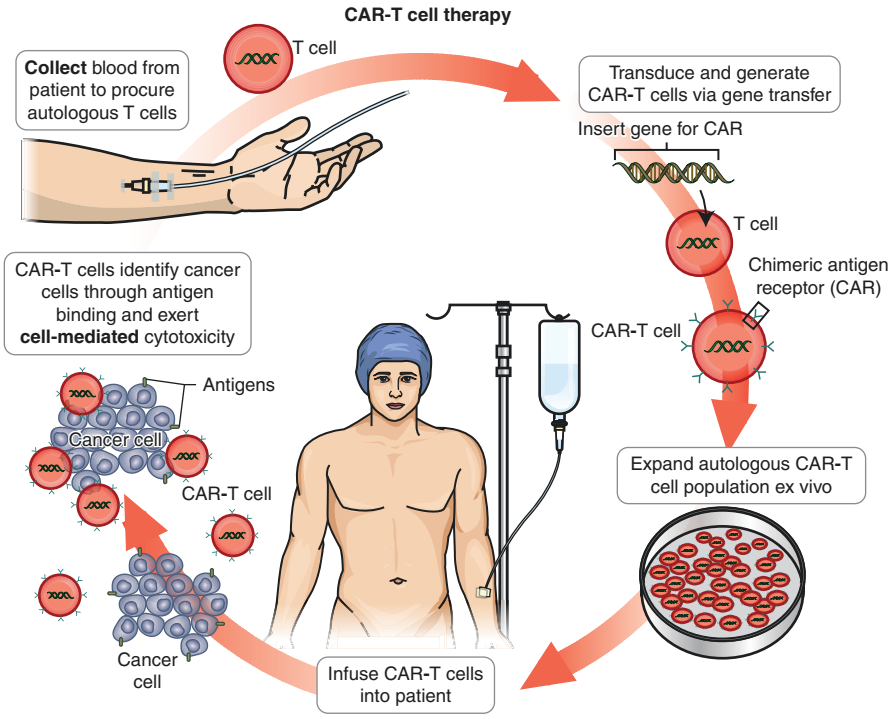

Fig. 3.1 CAR-T cell production. The general process for chimeric antigen receptor T cell (CAR-T cell) production and clinical application into patients. The general process takes approximately 2–4 weeks from the collection of blood from the patient to the reintroduction of the finished CAR-T cell product back into the patient

antigen-binding ability of monoclonal antibodies with the tumoricidal faculties and self-renewal property of T cells. They possess a major advantage over normal T cells in that they eradicate tumor cells independently of the major histocompatibility complex (MHC), which is commonly downregulated or is defective within tumor cells. They also possess the added advantage over allogenic stem cell transplants in that CAR-T cells are a completely autologous system of immunotherapy, thereby largely circumventing potential graft versus host disease risk (Fig. 3.2).

Clinical experience with CAR-T is predominantly with CD19-directed CAR-T therapy in ALL or B cell NHL, since CD19 is an attractive target due to its expression being relegated to B cells and not expressed in other normal human tissues elsewhere. However, since CD30 is universally expressed in HL, ALCL, certain DLBCL subtypes, T cell, and NK/T cell lymphomas, CAR-T directed against it has risen as a potential avenue for therapy. The aforementioned success of brentuximab also further strengthened the viability of such a CD30-targeted approach with CAR-T immunotherapy. Preclinical studies with EBV-specific cytotoxic lymphocytes (EBV-CTLs) being transduced to also express CD30-targeting CAR

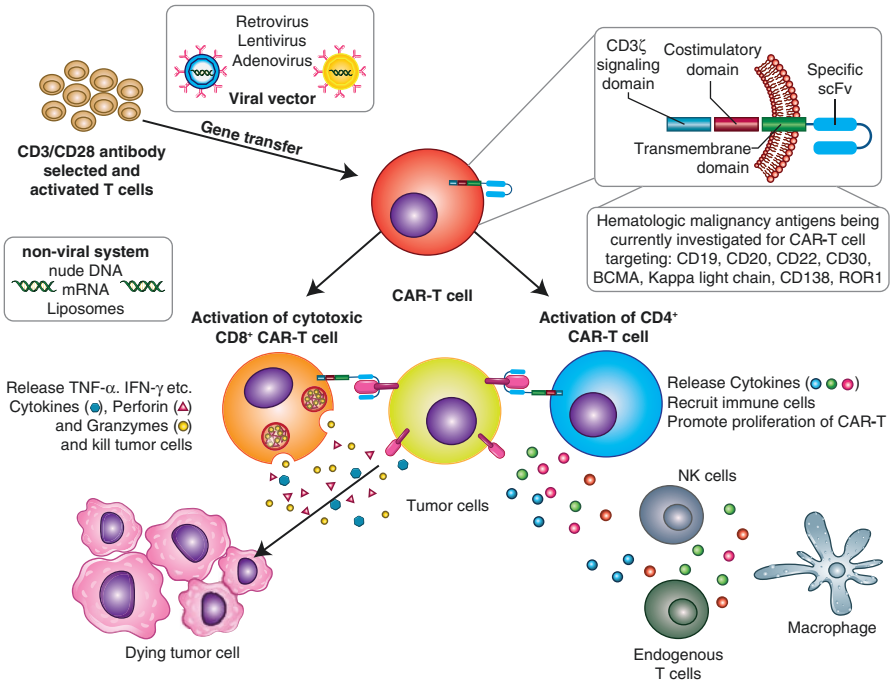

Fig. 3.2 CAR-T cell engineering. Molecular schemata of CAR-T cell generation. (**a**) T cells separated from the blood of the patient are first activated with CD3/CD28 antibodies in culture. (**b**) The gene containing the CAR construct is then transferred into the T cells via a viral vector, usually utilizing either lentivirus or retrovirus. Nonviral vectors with transposon or mRNA electroporation are occasionally used as well. (**c**) After genetic transfer of the CAR construct gene, T cells are able to express the CAR construct on their cell surface. The CAR construct contains an extracellular antigen-binding scFv fragment derived from a monoclonal antibody, which then connects to intracellular signaling domains via a transmembrane domain. Second-generation and more modern CAR-T cell iterations contain at least 1 co-stimulatory domain in addition to the CD3ζ signaling domain. (**d**) A mixture of CD4 and CD8 CAR-T cells are generated through the molecular reengineering process, each of which engages in tumor cytotoxicity either directly or indirectly

(CD30.CAR) showed great efficacy in eradicating autologous EBV+ cHL cells through their native TCR and EBV-/CD30+ HL cells through the CD30.CAR in a xenograft murine model [94].

These promising findings eventually led to a phase I dose escalation study in which seven patients with relapsed/refractory cHL and two patients with relapsed/refractory ALCL were infused with autologous CD30.CAR-T containing the CD28 endodomain [95]. Six of the cHL patients and one ALCL patient had previous brentuximab exposure prior to the CD30.CAR trial. There were three dose levels, from 0.2×10^8 to 2×10^8 CD30.CAR-T/m^2. Genomic quantitative PCR (qPCR), used to detect the persistence of the infused CD30.CAR-T, showed that the CD30.CAR-T cells reached a peak after 1 week post-infusion with a subsequent slow decline over the ensuing 4–5 weeks. However, six patients continued to have detectable CD30.

CAR-T 6 months post-infusion. Out of the seven relapsed/refractory cHL patients, two patients demonstrated CR lasting greater than 2 years, with one of those patients in continued CR after 2.5 years. Three other patients had transient stable disease (SD) lasting at least 6 weeks. Of the two relapsed/refractory ALCL patients, one had a CR lasting 9 months after receiving four infusions of CD30.CAR-T cells. There were no toxicities reported that were deemed attributable to the CAR-T cells, including no reports of cytokine release syndrome. Of note, none of the patients received lymphodepleting conditioning chemotherapy, which may have contributed to the lack of overall adverse events and also the lower number of overall responses.

Another phase I trial enrolled 18 relapsed/refractory patients, 17 of whom had cHL and 1 had cutaneous ALCL [96]. Five of these patients were brentuximab refractory. They received CD30.CAR-T with a 41BB endodomain at intended total doses varying from 1×10^7 to 3×10^7 CAR-T/kg. The patients received one of three forms of conditioning chemotherapy regimens of either fludarabine-cyclophosphamide, gemcitabine-mustargen-cyclophosphamide, or nab-paclitaxel-cyclophosphamide. qPCR was again used to detect the persistence of CD30.CAR-T, which showed similar peak levels of CAR-T cells at 6–9 days and decreasing to negligible levels 4–8 weeks post-infusion. In total, seven patients achieved a PR and six had SD with a median PFS of 6 months. Two of the PR patients who had received a second infusion of CD30.CAR-T had ongoing PR after 12+ months. No statistical difference was detected between the three different conditioning chemotherapy regimens, though all three regimens caused varying levels of cytopenias in all patients. One patient had grade 3 toxicity with liver transaminase abnormalities, and one patient had grade 4 cardiac toxicity felt to be more due to receiving a high dose of cumulative anthracycline in the past. The most common CAR-T-related adverse events were nausea and vomiting (28%), urticarial-like rash (11%), followed by breathlessness, psychiatric disturbances, and pneumonitis (all ~6%). These adverse events mostly occurred 1–3 weeks post-infusion. The levels of various cytokines were also measured, such as TNFα, IL2, IL4, IL6, and IL12. While there was a significant increase in TNFα and IL12 1-week post-infusion of CAR-T, it did not correlate with the observed clinical responses of patients. The other cytokines did not show any dramatic change in levels.

Several CD30.CAR-T clinical trials are underway currently to further investigate its efficacy (Table 3.1). While the published results are suboptimal to date, they do offer optimism as a potential avenue for treating relapsed/refractory CD30+ disease. Preclinical studies investigating how to augment efficacy show promise in improving the functionality of CD30.CAR-T. Since almost 40% of Hodgkin patients express EBV-associated antigens on their RS tumor cells, the aforementioned technique of altering EBV-CTLs to express a concurrent CD30.CAR alongside the native EBV antigen-targeting TCR could be a modality in improving the treatment of cHL [94]. Another innovative approach by the same research group tested methods of improving the homing mechanisms of CD30.CAR-T. RS cells are known to produce the chemokines CCL17 (also known as thymus- and activation-regulated chemokine or TARC) and CCL22 (also known as macrophage-derived chemokine or MDC). CCL17 and CCL22 attract Th2 cells and Tregs via binding to their chemokine receptor CCR4,

Table 3.1 Ongoing CD30.CAR trials. A list of ongoing clinical trials both in the United States and internationally with CD30-targeting CAR-T cell therapy

ClinicalTrial.gov identifier	Study title	Lymphoma subtypes included in trial	Institution/location
NCT03049449	T Cells Expressing a Fully Human Anti-CD30 CAR for CD30-Expressing Lymphomas	CD30+ HL, ALCL, and NHL	National Cancer Institute, Bethesda, MD, USA
NCT02917083	CD30 CAR-T Cells, Relapsed CD30-Expressing Lymphoma (RELY-30)	CD30+ HL, ALCL, and NHL	Baylor College of Medicine; Houston Methodist Hospital; Texas Children's Hospital, Houston, TX, USA
NCT02274584	CAR-T cells Targeting CD30-Positive Lymphomas (4SCAR30273)	CD30+ HL, ALCL, and NHL	University of Florida, Gainesville, USA; Peking University Cancer Hospital, Beijing, China
NCT02690545	Study of CD30 CAR-T Cell Therapy for Relapsed/Refractory CD30+ HL and CD30+NHL	CD30+ HL, ALCL, and NHL	Lineberger Comprehensive Cancer Center at University of North Carolina at Chapel Hill, NC, USA
NCT02663297	Administration of T Lymphocytes for Prevention of Relapse of CD30+ Lymphomas After High-Dose Therapy and Autologous Stem Transplantation	CD30+ HL, CD30+ NHL, or CD30+ lymphoproliferative disorders	Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, USA
NCT02958410	Study of CD30-Targeted CAR-T Cells in Lymphoid Malignancies	CD30+ HL, ALCL, and NHL	Southwest Hospital of Third Military Medical University, Chongqing, China
NCT02259556	CD30-Directed CAR-T Cell (CART30) Therapy in Patients with Relapsed and/or Refractory CD30-Positive Lymphomas	CD30+ HL, ALCL and NHL	Chinese PLA General Hospital, Beijing, China
NCT03383965	A Clinical Study of CD30 Targeted CAR-T in Treating CD30-Expressing Lymphomas	CD30+ HL, ALCL, and NHL	Weifang People's Hospital Weifang, Shandong, China

where these cells then help to create an immunosuppressive tumor microenvironment around the RS cells. Conversely, cytotoxic CD8+ effector cells lack CCR4, resulting in a chemokine receptor mismatch and inability to traffic across the CCL17/CCL22 gradient. This paucity of tumoricidal cellular elements within Hodgkin lymphoma sites contributes to the hampered inflammatory immune response to HL. Preclinical experiments have also examined reengineering CD30.CAR-T cells to forcibly express

CCR4. These modified CCR4-CD30.CAR-T demonstrated enhanced migration to tumor sites and augmented tumor cytotoxicity in mice engrafted with human HL [97]. Incorporating these mechanisms, along with the exploration of additional cellular processes, could help boost and improve CD30.CAR-T efficacy.

PD-1 Checkpoint Inhibitors

PD-1 is an inhibitory receptor expressed by activated T cells on the cell surface [98]. It has two ligands, PD-L1 and PD-L2, which are highly overexpressed in several solid tumors and hematological malignancies. The chromosomal locus 9p24.1 contains the genes for PD-L1 and PD-L2. Studies show cHL RS cells possessing aberrations in the PD-1/PD-L1 pathway, exhibiting copy number gains of 9p24.1 which correlated with increased PD-L1/L2 expression in RS cells [25, 26]. In addition, the same 9p24.1 locus contains the gene for JAK2, and increased JAK2 expression has been shown to generate increased PD-L1/L2 expression as well [25]. Furthermore, tumor-associated macrophages can accumulate at lymphoma sites and also upregulate their PD-L1 expression, synergistically enriching immunosuppression within the tumor microenvironment [27]. As a result, studies have begun investigating PD-1 checkpoint inhibition, primarily with pembrolizumab and nivolumab. They are both anti-PD-1, humanized IgG4, PD-1 blocking antibodies which have FDA approval for use in solid malignancies such as melanoma and non-small cell lung cancers.

Nivolumab was first examined in a phase I report with relapsed/refractory cHL patients. The ORR in 23 patients was 87% with a CR rate of 17% [28]. A subsequent single-arm phase II study with 80 patients who had also previously failed both auto-SCT and brentuximab treatments showed an ORR 66% with CR rate of 8.8% at a median follow-up of 8.9 months [29]. PFS and OS at 6 months were 77% and 99%, respectively, with an estimated median duration of response of 7.8 months.

Not surprisingly, pembrolizumab has displayed similar levels of efficacy as nivolumab in cHL studies. A phase II trial with 210 relapsed/refractory patients demonstrated ORR of 69% with a CR rate of 22.4% [30]. On subgroup analysis, patients who had relapsed after auto-SCT and BV treatments showed an ORR of 74% and CR rate of 22%. Patients who were ineligible for auto-SCT but received BV had ORR and CR rates of 64% and 25%, respectively. Those who had received an auto-SCT but no BV had ORR and CR rates of 70% and 20%, respectively. The estimated 9-month PFS and OS rates were 63% and 98%, respectively.

Based on the preceding promising results, further trials are underway to implement these checkpoint inhibitors. One ongoing phase III trial is comparing the combination of nivolumab and BV to BV alone in relapsed/refractory patients who are either post-auto-SCT or transplant ineligible (NCT03138499). Another phase III study in progress is investigating pembrolizumab in comparison to BV in relapsed/refractory cHL patients (NCT02684292). Currently, checkpoint inhibition with nivolumab or pembrolizumab is FDA approved in the relapsed/refractory setting and especially represents a viable treatment alternative for patients who have failed auto-SCT and/or BV (Fig. 3.3).

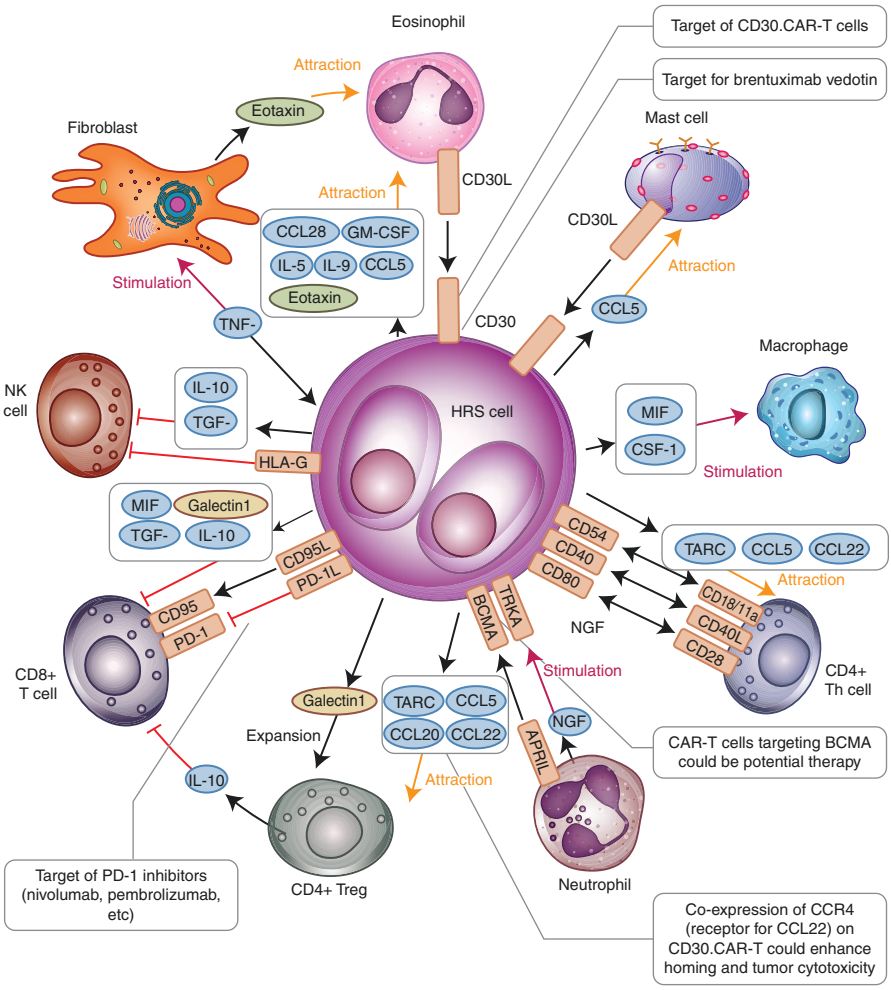

Fig. 3.3 Immunosuppression and immune targets in Hodgkin lymphoma. Hodgkin Reed-Sternberg (HRS) cells employ a variety of immunosuppressive mechanisms within the tumor microenvironment, including cytokine secretion and inhibitory cell surface marker expression. Some of these mechanisms and markers can be targeted by CAR-T cells or other immunotherapies

Conclusion

cHL and ALCL are generally associated with a very good prognosis and high cure rate with frontline therapy. Salvage chemotherapy with auto-SCT offers additional, high chance of cure in the minority of patients that do relapse or are refractory. However, until recently there were very limited treatments for patients with multiple relapsed/refractory disease, with available options only providing very short-term disease control and inevitable relapse. With the advent of new biologic and cellular

immunotherapies targeting CD30 like brentuximab and CAR-T, there has been a significant expansion in the treatment armament for these diseases. Clinical trials with these agents have shown great promise and, in the case of brentuximab, have already been approved for use in patients for both frontline and second-line treatments. CD30-directed immunotherapy has also expanded beyond use in cHL and ALCL to other NHL subtypes that occasionally also positively express CD30. With such a potentially broad spectrum of relapsed/refractory lymphoma to treat, CD30-directed immunotherapy can have extensive clinical utility and tangible long-term efficacy and represent a very viable modality for exerting excellent disease control and potential cure for these patients in the very near future.

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