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Immunotherapies for Hodgkin's lymphoma

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Abstract

Multiple immune evasion strategies characterize the pathobiology of Hodgkin's lymphoma. These must be considered when developing and testing immunotherapeutic approaches for this disease. The clinical experience with adoptive immunotherapy of Epstein–Barr virus positive tumors, and with monoclonal antibodies directed against CD30, CD20, and other antigens, is herein reviewed.

Keywords

Hodgkin's lymphoma; Immunotherapy; Epstein–Barr virus; Rituximab; CD30

1. Introduction

The immunotherapy of Hodgkin's lymphoma (HL) has been especially challenging because of a combination of host and tumor factors. Intrinsic T cell defects and anergy are commonly associated with HL. There is the global immunosuppression from the lymphoma itself and from the agents used to eradicate it. Interactions within the tumor microenvironment are complex [1] and a variety of immune evasion strategies may be at play. The dense infiltrate of benign, mostly CD4+ T cells that surround the malignant Hodgkin/Reed–Sternberg (H/RS) cells, and that comprise almost all of the tumor, are enriched for inhibitory T-regulatory cells [2]. The cytokines and chemokines produced by tumor tissue, including TGF-B, IL-10, and the chemoattractant TARC, may all favor a Th2-type T cell response [3–5]. Additionally, expression of FAS ligand, RCAS1, and other receptors by RS cells may induce apoptosis of activated cytotoxic T cells and natural killer (NK) cells [4,6]. These and other factors might limit the effectiveness of cell-mediated immune responses and contribute to the persistence of the malignancy [3–5]. Herein we review the progress with immunotherapeutic approaches to HL, with a focus on those strategies that have been studied clinically.

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2. Targeting Epstein–Barr virus

2.1. Tumor-associated antigens

Approximately 25–50% of cases of classical HL are associated with the presence of Epstein–Barr virus (EBV) in the RS cells [7–10]. In EBV-associated malignancies including a subset of classical HL, EBV antigens are virtually tumor-specific and have been established as immunotherapeutic targets [11]. In contrast to the broad antigen expression seen in posttransplant lymphoproliferative disease (PTLD), HL expresses a restricted pattern of viral latency genes: Epstein–Barr nuclear antigen 1 (EBNA1), and the transmembrane proteins, latent membrane proteins 1 and 2 (LMP1 and LMP2) [12].

An interesting research focus is the adoptive immunotherapy of EBV+ HL. The success of this approach requires that EBV-specific cytotoxic T lymphocytes (CTL) be generated and potentially amplified, and that RS cells be susceptible to cell-mediated killing [13]. Unlike most EBNAs (EBNA 2, 3A, 3B, and 3C), which usually can generate strong CTL responses in healthy individuals with a variety of HLA backgrounds, the antigens expressed in HL are not immunodominant antigens [14,15]; responses to these antigens are weak or undetectable. This may very well complicate the development of immunotherapies. Nevertheless EBNA1 and LMP2 in particular have received attention as promising CD4+ and/or CD8+ T cell targets in EBV-associated malignancies [16,17]. EBNA1, although recognized as a CD4+ T cell target antigen, was long regarded as “immunologically invisible” to cytotoxic T cells, in part because its glycine–alanine repeat was thought to prevent endogenous processing for MHC class I presentation [17]. However this has been recently challenged [18,19], and EBNA1 has received renewed interest as a potential CD8+ T cell target.

LMP1 and 2 are the major targets for immunotherapeutic strategies that involve CD8+ effector cells, with LMP2 being better characterized. It has been established that LMP1 and LMP2 are expressed at high levels in RS cells and their variants [20]. Importantly, however, they are not effectively targeted by CTL in patients. The presence of an ongoing, yet ineffectual, immune response is suggested by the polymorphous infiltrate in EBV+ HL; this is mostly comprised of T cells, some being EBV-specific although generally targeting viral antigens not expressed in tumor [21,22]. Yet preclinical and clinical data suggest that EBV+ HL is potentially susceptible to immunotherapy. EBV-specific CTL or CTL precursors have been detected in the blood of EBV+ HL patients [13,20,21,23]. When HL cell lines were engineered to express viral antigens, they were susceptible to immune killing *in vitro*[13]. However, EBV-specific cytotoxicity has been found to be absent or blunted in cultures from patients with EBV+ compared with EBV– HL [21]. This does not appear to be explained by defective antigen presentation or an inherent resistance to class I killing; EBV+ HL tumor cells usually express high levels of MHC class I (in contrast to most cases of EBV– HL), with intact class I antigen presentation machinery [20,24]. Local suppression of T cell responses might be a key pathogenetic factor [21], for example through cytokines, chemokines, immune evasion molecules, T-regulatory cells [2], and/or other mediators.

There is a literature describing strain variation and mutations in the LMP1 gene [25], which may make targeting this antigen more difficult. Although LMP2 escape mutations have been documented in PTLD, LMP2 rarely shows escape mutations in HL [20,26].

2.2. Adoptive immunotherapy

CTL are important in controlling EBV infection. Adoptive cellular immunotherapy has thus been investigated for the prevention or treatment of EBV-associated PTLD arising after marrow or solid organ transplantation [11,27–29]. For example, in allogeneic marrow transplant recipients with EBV+ PTLD, infusion of donor leukocytes (which should include T cells presensitized to the virus) has produced sustained clinical responses in a small number of patients [28]. Also reported is regression of PTLD after infusion of donor-derived, *ex vivo* expanded, polyclonal EBV-specific CTL [11]. Impressively, in a recently reported multicenter study of 33 cases that failed conventional therapy, serial infusions of allogeneic, partially HLA-matched EBV-specific CTL from a CTL bank produced objective responses in 52% at 6 months [29]. Interestingly the rate of decline in EBV viral load did not correlate with tumor response [29]. In advanced stage nasopharyngeal carcinoma (an EBV-associated tumor), infusion of autologous EBV-specific CTL has also induced antiviral immunologic responses and objective clinical responses [30,31].

A similar strategy has been translated to the investigation of EBV + HL, with antitumor activity demonstrated in some cases. Peripheral blood from HL patients was initially used to create both an EBV-specific CTL line and B-lymphoblastoid cell line (LCL, an EBV-transformed cell line). The EBV-specific CTL were activated *in vitro* using LCLs as antigen presenters, then expanded, genetically marked, and reinfused into patients [32,33]. Patient-derived CTL expanded less easily and had lower T cell receptor zeta chain expression than CTL from healthy donors, but had comparable cytotoxicity against EBV *in vitro* [33]. After reinfusion, the CTL expanded further, persisted in the blood for up to 12 months, and trafficked to tumor sites. They appeared to enhance the cellular immune response to EBV, with decreases in viral load [33]. Of 11 patients with measurable disease, 3 objective responses occurred after CTL infusion [32].

A potential limitation of using autologous LCLs for antigen presentation is that T cells specific for immunodominant EBV antigens or early lytic cycle antigens (which are not expressed in HL) are preferentially amplified [34]. Nevertheless, the CTL lines generated with this approach contained small populations of LMP2-specific clones [33]. The question arises as to whether CTL specific for LMP2 might be more effective than polyclonal EBV-CTL in the adoptive immunotherapy of HL [35]. CTL specific for LMP1 [36] or for LMP2 [37,38] have been successfully generated. One approach is to stimulate patient T cells using autologous dendritic cells and LCLs, both overexpressing LMP2A through an adenoviral vector [34]. This can generate large numbers of LMP2-specific CD4+ and CD8+ T cells [34]. In a study of 16 patients with EBV+HL or non-Hodgkin's lymphoma who had relapsed or were at high risk of relapse, infusion of such autologous LMP2-CTL was well tolerated and was associated with an increased frequency of LMP2-CTL in the blood [39]. Clinical activity was demonstrated, including objective responses in 5 of 6 patients who had had detectable tumor. Responses lasted a minimum of 9 months, and 4 of those responses were complete. Outcomes are therefore encouraging particularly given the favorable toxicity profile, and further study in HL and other EBV+ tumors would be of interest.

Another approach that has been investigated in HL is infusion of EBV-CTL from allogeneic, partially HLA-matched donors [39]. In a pilot study, 6 relapsed/refractory HL patients

received the infusions either alone or after fludarabine to facilitate engraftment. Donor lymphoid chimerism was not detected. Therapy was well tolerated but clinical activity modest or absent; the 5 patients with more than minimal residual disease progressed shortly (2–7 months) after CTL infusion.

Adoptive immunotherapy of HL could be enhanced after initial lymphodepletion with chemotherapy [40]. Diverse approaches have been investigated preclinically to overcome immune evasion strategies of the tumor and enhance the adoptive immunotherapy of EBV+ HL. Examples include the genetic modification of EBV-CTL to promote resistance to TGF-B [41], to express immunostimulatory cytokines [42], or to express antitumor chimeric T cell receptors [43,44].

2.3. Vaccines

The development of cancer vaccines is particularly challenging in HL, given the multiple barriers to successful immunotherapy. There is as yet a paucity of clinical experience with vaccines in this disease. However, the feasibility of vaccines for EBV-associated tumors is exemplified by a clinical trial of an EBV peptide-pulsed dendritic cell vaccine for nasopharyngeal carcinoma; epitope-specific cellular vaccine responses were elicited or augmented in over half of patients, and in a minority this was associated with partial reduction in tumor burden [45]. An LMP1 polyepitope vaccine has been investigated preclinically, with induction of CTL responses and antitumor activity in murine models of LMP1-expressing tumors [46]. Dendritic cells, infected by vaccinia virus expressing EBNA1-LMP2 fusion protein, have *in vitro* reactivated both CD4+ and CD8+ memory T cells from EBV seropositive donors [47]. EBV vaccine strategies have been or are currently being explored in at least several clinical trials targeting nasopharyngeal carcinoma and other EBV-associated tumors including HL.

3. Targeting CD30

Antibodies directed against CD30 have been in clinical trials for years [48] and continue to be investigated in phase I or II trials (Table 1). A wide array of compounds has been developed and tested, largely in cell lines and murine models. Relatively few trials have thus far been published. In addition to naked monoclonal anti-CD30 antibodies, bispecific antibodies, radioimmunoconjugates, and antibody–toxin conjugates have been evaluated in patients with relapsed or refractory HL as well as other CD30 positive malignancies, such as anaplastic large cell lymphoma.

3.1. CD30 in Hodgkin's lymphoma

The CD30 receptor, a lymphocyte activation marker and member of the tumor necrosis factor (TNF) receptor superfamily, is consistently overexpressed by H/RS cells. This in combination with its limited expression in normal lymphoid tissue [49] makes it a rational therapeutic target.

In contrast to CD30, whose expression in nonmalignant cells is largely restricted to activated normal or virus-infected lymphocytes, the CD30 ligand (CD30L) is expressed by a variety of hematopoietic cells [50]. CD30 has pleiotropic functions and has been linked to cell cycle

regulation and apoptosis, including the negative selection of autoreactive lymphocytes [51]. The precise functions of this antigen in normal and malignant cells remain to be clarified. Depending on the type of cell line and the context, CD30 signaling has had pro-apoptotic, antiproliferative, or even proliferative effects [50,52]. Deregulation of NF-kB activity is a common feature in HL [53], and CD30 signaling has been implicated as a mechanism driving constitutive NF-kB activation in this disease [50]. It has been proposed that CD30 overexpression can drive such signaling in a ligand-independent manner through self-aggregation [53]. CD30/CD30L interactions involving H/RS cells and benign cells in the tumor microenvironment have also been postulated to have a pathophysiologic role [54].

3.2. Unconjugated anti-CD30 antibodies

SGN-30 (cAC10) is a chimeric monoclonal antibody against CD30 that has been investigated in the phases I and II setting. Despite the promising preclinical activity of this drug [55], its clinical activity in patients with relapsed/refractory HL has been limited (Table 1). A phase I study in relapsed/refractory CD30+ hematologic malignancies demonstrated that a single dose was safe and generally well tolerated [56,57]. In the phase II portion of a subsequent multidose phase I/II study [58,59], some disease stabilizations but no remissions occurred among 35 evaluable, heavily pretreated HL patients [59], and the HL arm was therefore closed [60].

Antibodies with murine components may lead to the generation of neutralizing antibodies, which may reduce efficacy and limit retreatment [61]. Human antibodies are also generally better than murine antibodies in recruiting immune effector mechanisms such as antibody-dependent cellular cytotoxicity [62]. 5F11 (MDX-060) is a fully humanized monoclonal antibody that recognizes a different CD30 epitope than does SGN-30 [63]. Based on promising *in vitro* and *in vivo* data [62], the drug advanced to clinical testing (Table 1). In heavily pretreated patients with relapsed or refractory CD30+ lymphomas, a multicenter phase I/II trial demonstrated a favorable toxicity profile [64]. Clinical activity was however modest, with objective clinical responses occurring in 4 of 67 HL patients. Some of these patients were taking steroids concomitantly although this was not felt to contribute to the response [64]. Additional patients had disease stabilization. The drug is undergoing further phase II testing, with a trial opened in late 2005 comparing MDX-060 plus dexamethasone, MDX-060 plus gemcitabine, and gemcitabine alone in relapsed/refractory CD30+ malignancies. Second generation anti-CD30 antibodies that have the potential for improved antitumor activity are being investigated preclinically [65].

Preclinical data suggest that there is a potential role for drug-CD30 antibody combinations. For example, *in vitro* data suggest that the anti-tumor activity of 5F11 is limited because of CD30-mediated activation of NF-kB and its target, c-flip [66]. In an HL cell line, evidence of enhanced NF-kB activation was likewise seen shortly after treatment with SGN-30 [67], which could in turn increase chemotherapeutic resistance. In tumor cell lines and an HL xenograft model, giving bortezomib (a proteosome inhibitor that suppresses NK-kB activation) after 5F11 helped to overcome apoptotic resistance and had cytotoxic synergy [66]. *In vitro* data also suggest enhanced cytotoxicity when 5F11 is combined with chemotherapy including gemcitabine and etoposide [68]. Similarly, SGN-30 has been found

to sensitize tumor cells to a variety of cytotoxic agents; significant synergy with bleomycin, etoposide, and cytarabine was found *in vitro*, and potentially enhanced antitumor activity was noted with bleomycin in HL xenografts [67]. A randomized phase II trial planning a comparison of combination chemotherapy (gemcitabine, vinorelbine, and liposomal doxorubicin) plus SGN-30, versus chemotherapy plus placebo, has opened through the CALGB for HL patients with relapsed/refractory disease.

Many reasons can be envisioned for the modest activity seen to date with this type of therapy. Some include the fact that CD30 antibodies have had quite variable effects on cell proliferation and apoptosis depending on the preclinical model, including potentiation of NF-kB activity in some cases. The particular epitope of CD30 may be clinically relevant in this regard. Cytokines in the tumor microenvironment and the presence of T-regulatory cells could also very well be factors, as is the case when considering immunotherapies for HL in general. Insufficient drug delivery may be a barrier given that the malignant RS cells comprise a tiny fraction of the tumor mass, and also given that patients with active HL can have high serum levels of soluble CD30 [69]. Soluble CD30 has been described in almost half of HL patients with active disease, with higher incidence and level of detection in those with advanced stage or progressive disease [69]; another study involving multiply relapsed HL found detectable soluble CD30 in all patients [70]. As with other types of immunotherapies, one could postulate that clinical activity of anti-CD30 monoclonal antibodies might be enhanced after cytoreduction with other agents. Another recently reported strategy in EBV+ HL, which has generated promising data in murine xenograft models, is the genetic modification of EBV-specific CTL to express a chimeric antigen receptor for CD30 [44].

3.3. Anti-CD30 immunoconjugates

To enhance the effectiveness of CD30-directed therapies, many CD30 antibody–drug conjugates have been developed. Most of the data are preclinical, with a few of the drugs having entered clinical trials. Clinical experience with anti-CD30 conjugated to saporin (a ribosome-inactivating protein) is summarized in Table 1 [48,71]. As a more recent example, SGN-35, a chimeric anti-CD30 antibody (SGN-30) conjugated to a new anti-mitotic agent, demonstrated potent cytotoxicity in CD30+ tumor cell lines and resulted in tumor regressions in murine xenograft models [72,73]. It has therefore advanced to a phase I dose-finding study in patients with relapsed/refractory CD30+ hematologic malignancies including HL.

A wide variety of antibody–drug fusion proteins has also been investigated *in vitro* and in murine models of HL. These generally involve CD30 antibody linked to cytokines (IL-2 [74], IL-12 [75]) or to toxins [76–78]. Few early phase trials have been conducted [48,61]. A phase I study of a murine anti-CD30 antibody linked to deglycosylated ricin A-chain was conducted in heavily pretreated patients with CD30+ malignancies and reported in 2002 [61]. Of 15 evaluable patients (all but one having HL), there was 1 PR, 1 minor response, and 2 disease stabilizations. Seven of 17 patients developed human anti-ricin antibodies, and one developed human anti-mouse antibodies (HAMA). Vascular leak syndrome was dose-

limiting, and the maximum tolerated dose was lower than that observed with other similar immunotoxins [61].

Bispecific antibodies have also been under development for HL [79–81] (Table 1). Two older clinical trials of a murine anti-CD16/CD30 bispecific antibody were conducted in an attempt to enhance effector functions against the tumor. Crosslinking of CD16 (Fcγ receptor III) on NK cells induces NK activation and lysis of CD30+ tumor cells *in vitro*, and the bispecific antibody leads to tumor regressions in murine models [80]. In a phase I trial, the bispecific antibody induced 2 objective responses (excluding minor or mixed responses) out of 15 relapsed/refractory patients [79]. The drug was generally well tolerated, although allergic reactions occurred with attempted retreatment. HAMA developed in 60% despite patients being heavily pretreated. In a follow-up study of 16 patients, those with at least stable disease to the first course of antibody, administered intermittently or by continuous infusion, received IL-2, followed by antibody and GM-CSF with the goal of augmenting NK cell numbers and cytolytic activity [80]. Antitumor activity was confirmed, with objective responses in 25% lasting up to 9 months, and an additional 25% having disease stabilization. The contribution of the dosing schedule (most of the responses occurred with the continuous infusion) and the cytokines remains to be clarified. Manufacturing constraints have been a barrier to defining the maximum tolerated dose and to conducting larger studies, although follow-up studies of bispecific antibodies, particularly with less immunogenic constructs, would be of interest.

Another bispecific antibody, H22 × Ki-4, has similarly produced objective but short-lived responses in a small phase I trial for relapsed/refractory HL [81]. This construct has murine anti-CD30 antibody linked with a humanized antibody against CD64 (FcγRI, the high-affinity Fc receptor for IgG that is expressed by phagocytes and activated neutrophils) [82]. The construct might therefore enhance recruitment of effector cells, and has been found to mediate phagocytosis and antibody-dependent cellular cytotoxicity in CD30+ tumor cell lines [82]. In 10 heavily pretreated HL patients, objective responses, lasting 1–5 months, occurred in 25%, with additional patients having disease stabilization. Human anti-globulin antibodies developed in most cases. In addition to the study of less immunogenic constructs, trials of bispecific antibody combined with immunostimulatory cytokines might be considered.

3.4. Radioimmunotherapy

An approach that has been recently investigated is the conjugation of anti-CD30 antibody with a radioisotope, given that HL is typically a radiosensitive tumor [83]. Clinical experience with radioimmunotherapy in HL had previously centered upon polyclonal antiferritin antibodies conjugated to either ^{131}iodine or ^{90}yttrium. Radiolabeled polyclonal antiferritin antibodies, with or without autologous stem cell infusion, have been investigated clinically in a number of early phase trials [84–89] based on the finding that ferritin is a tumor-associated antigen [90]. These early phase, generally older trials, published in the mid-1980s and 1990s, demonstrated some antitumor activity in the relapsed/refractory setting. In heavily pretreated patients, response rates of roughly 40–60% were typical, with median response durations on the order of 6–8 months [85]. For example, in an analysis of

134 end-stage HL patients enrolled in 5 consecutive studies of polyclonal ^{90}yttrium-labeled antiferritin, a response rate of 60% and average response duration of 8 months was described [91]. The main toxicity was hematologic. Responses occurred more often in patients with smaller tumor volumes, with one-third of relapses occurring in previously uninvolved sites. Similarly, in a group of 90 patients with relapsed HL (median of 4 prior therapies, with 75% having failed stem cell transplantation), response rates ranging from 20% to 86% were achieved depending on dose and timing; fractionation did not reduce hematologic toxicity or improve the antitumor effect [87]. More recently, a study of 10 patients with relapsed/refractory HL treated with ^{90}yttrium-labeled antiferritin antibody was reported [89]. The toxicity profile, overall response rate of 70% (on intent-to-treat analysis), and median response duration of 8 months mirror the results of earlier investigations.

In the pilot study of anti-CD30 based radioimmunotherapy for relapsed/refractory HL, murine anti-CD30 antibody was conjugated to ^{131}iodine, as this approach permits dosimetry and biodistribution assessments [83]. The 22 patients were heavily pretreated; most had received radiation and autologous stem cell transplantation, and approximately one-third had relapsed within several months of first-line treatment. Soluble CD30 was detectable in all patients at baseline and was blocked by preinfusion of native antibody. The overall treatment was generally well tolerated with mainly hematologic toxicity, which was delayed, as is the case with ^{131}iodine tositumomab and ^{90}yttrium ibritumomab tiuxetan in non-Hodgkin's lymphomas. The median time to platelet and neutrophil count nadir was 5 weeks, with severe myelosuppression notably occurring in one-third. HAMA developed in 18% by a week after treatment, with significant impact on residence time. Antitumor activity was seen, with an overall objective response rate of 27% and median response duration on the order of a few months (Table 1). Interestingly, visualization of tumor on scintigraphy occurred in only 4 patients and did not predict clinical response. Similarly, in a previous pilot study of 6 patients treated with a ^{131}iodine-anti-CD30 [92], only half of tumor sites were visualized, although binding was evident by immunohistochemistry in all biopsied sites. Further investigations of radioimmunotherapeutic approaches to HL, including combined modality approaches using antibody constructs with less immunogenicity, would be of interest.

4. Other immunoconjugates

In early phase, older studies, recombinant immunotoxins for relapsed CD25+ malignancies, namely diphtheria toxin moieties linked to IL-2 [93] or truncated pseudomonas exotoxin linked to anti-CD25 [94], have had limited or no clinical activity in HL. A monoclonal antibody against CD25 (the α subunit of the IL-2 receptor), conjugated to ricin A-chain, has also been evaluated in early phase studies of relapsed/refractory HL (Table 1). Following a phase I study of 15 patients with relapsed/refractory HL [95], a study of 18 relapsed/refractory HL patients treated at the maximum tolerated dose was reported in 2000 [70]. Toxicities were in general moderate and included vascular leak syndrome, dyspnea, weakness, myalgias, and allergic reactions. Human anti-ricin antibodies and HAMA developed commonly in patients receiving more than one cycle. Modest clinical activity was noted in this heavily pretreated cohort, with two PRs, one minor response, and five disease stabilizations and an associated median time to progression of under 5 months.

5. Targeting CD20

It is only relatively recently that the B cell origin of RS cells in classical HL has been widely appreciated [96,97]. The origin of the RS cell had long been unclear in part because of the paucity of lymphocyte markers and the absence of surface immunoglobulin expression [98]. Immunoglobulin gene rearrangement studies importantly suggest that H/RS cells in classical HL represent a monoclonal expansion of a germinal center B cell [96,97]. Therefore B cell antigens may be therapeutic targets in HL. Phase II trials have indeed demonstrated that rituximab has activity in nodular lymphocyte-predominant as well as classical HL.

5.1. Rituximab in lymphocyte-predominant Hodgkin's lymphoma

CD20 is a rational therapeutic target in lymphocyte-predominant HL, given that the malignant RS cell variants characteristically express this antigen. The single-agent activity of rituximab has been described in small phase II trials of this disease [99,100]. In 14 patients with relapsed or progressive HL, including 10 cases of lymphocyte-predominant HL and 2 cases each of transformed lymphoma and CD20+ classical HL, 4 weekly infusions of standard-dose rituximab produced a 96% overall response rate (57% CR) [99]. Infusional toxicities, generally mild or moderate, occurred in most patients. At median 1 year follow-up, 75% of responders remained in remission.

Similarly, in another study of 22 patients with either treated or untreated lymphocyte-predominant HL, the same schedule of rituximab produced an overall response rate of 100% (46% CR/CRu) and was well tolerated [100]. However, response durations tended to be short; after 13 months median follow-up, 41% of patients had progressed, translating to an estimated median freedom from progression of 10 months. Of potential concern was that 2 of the 5 patients with biopsyproven disease progression had a large cell non-Hodgkin's lymphoma, raising the question of whether rituximab potentiates the risk of transformation.

5.2. Rituximab in classical Hodgkin's lymphoma

Most of the tumor in classical HL is comprised of a benign inflammatory infiltrate including B cells and activated T cells, with relatively few interspersed RS cells. In contrast to lymphocyte-predominant HL, the majority of cases of classical HL lack CD20 expression on the malignant cells. Nevertheless, evidence suggests that response to rituximab can occur regardless of the CD20 expression pattern [101,102]. In 22 patients with multiply relapsed classical HL, single agent rituximab (375 mg/m^2 weekly for 6 weeks) produced a partial or complete remission in 5 patients (22%), with a median response duration of nearly 8 months (range 3–15 months) [102]. Improvement in B symptoms was also reported. Rituximab has also been combined with standard chemotherapy for classical HL, with promising early data [101,103,104]. Rituximab (375 mg/m^2 weekly for 6 weeks) was given concurrently with, or begun 3 weeks prior to, ABVD in patients with newly diagnosed classical HL in an MD Anderson trial [101]. On initial report, all patients responded, with an estimated event-free survival of 83% after a median 21 month follow-up. However, only in 17% of cases in did the H/RS cells express CD20. On an updated interim analysis of 65 patients [103], poor-risk patients (International Prognostic Score [105] of at least 3) had an estimated event-free survival of 77%, versus 55% historically with ABVD alone. In 2 patients with pre- and post-

rituximab lymph node biopsies, rituximab resulted in complete depletion of CD19+ and CD20+ B cells from the tumor tissue by flow cytometric analysis [103]. Rituximab has also been investigated in combination with gemcitabine for relapsed and refractory classical HL [104]. The investigators suggested that rituximab may enhance the effects of cytotoxic chemotherapy by depleting benign B cells, and hence cytokines and intercellular signals, from the tumor microenvironment [101,104]. Such an effect would thus be independent of CD20 expression on the RS cells. Recent insights into the stem cell biology of classical HL point to another possible mechanism for rituximab [106]. Given its favorable toxicity profile, this drug warrants further investigation in classical HL.

6. Conclusion

There are many barriers to the successful immunotherapy of HL, and clinical experience has been relatively limited. However, HL is potentially susceptible to immune-mediated killing. There is also a clear need for more effective, but also minimally toxic, therapies for a subset of patients with this disease. Continued clinical investigation of immunotherapeutic strategies for both EBV+ and EBV− HL, particularly in less heavily pretreated patients, is encouraged. Further characterization of the interaction between the malignant cells and the tumor microenvironment should prove highly relevant in this regard.

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Table 1

CD30-directed therapy in relapsed or refractory Hodgkin's lymphoma

Reference	Drug	Study type	*N*	Prior therapies	CR+PR	Duration	MR+SD	Duration	Comments
Falini et al. [48]	Murine anti-CD30 linked to saporin (Ber-H2/SO6)	Pilot	4	NR	75%[a]	8–10 weeks	25%	6 weeks	All developed antibodies to Ber-H2 and immunotoxin.
Hartmann et al. [79]	Murine anti-CD16/CD30	Phase I/II	15	Median 4 (2–8); 47% post-SCT	2/16	3–6 months	33%	Median 2 (1-11+) mo	HAMA in 60% by 4 weeks.
Hartmann et al. [80]	Murine anti-CD16/CD30 +/− IL-2 and GM-CSF	Randomized pilot[b]	16	Median 3 (2–6); 88% post-SCT	25%	Median 6 (5–9) months	25%	Median 4 (3–6+) months	HAMA in 38% by 4 weeks.
Borchmann et al. [81]	Anti-CD64/CD30	Phase I	10	Median 4 (2–6); 90% post-SCT	40%	Median 2 (1–5) months	40%[d]	NR[e]	HABA increased in 80%.
Schnell et al. [61]	Murine anti-CD30 + ricin A-chain (Ki-4.dgA)	Phase I	17 (15 HL)	Mean 6 (2–9); 76% post-SCT	7% overall[c]	5 months	20% overall[c]	NR[f]	HARA in 41%, HAMA in 6%.
Schnell et al. [83]	^{131}Iodine-conjugated, murine anti-CD30 (^{131}I-Ki-4)	Phase I	22	Median 4 (2–6); 73% post-SCT	27%	Up to 6 months	18%	NR	Delayed grade 4 cytopenias in 32%. HAMA in 18% by day 7.
Bartlett et al. [56], Carabasi et al. [57]	SGN-30	Phase I	13 (9 HL)	Median 5 (1–9); 69% post-SCT	15% overall, 11% in HL	NR	NR	NR	Single dose ranging from 1–15 mg/kg. HACA in 8%.
Bartlett et al. [58][g]	SGN-30	Phase I	24 (21 HL)	Median 5 (2–10); 83% post-SCT	4% overall, 0% in HL	–	25% overall, 14 in HL	% NR	Part of a phase I/II study. Six weekly doses of 2–12 mg/kg.
Leonard et al. [59][g]	SGN-30	Phase II	35 evaluable[h]	Median 4 (1–7); 73% post-SCT	0%	–	26%	Mean 3.5 (2–7) months	Part of a phase I/II study. Six weekly doses of 6mg/kg or 12 mg/kg.
Ansell et al. [64]	MDX-060 (5F11)	Phase I/II	72 (67 HL)	Median 4 (1–12); 93% post-SCT	8% overall[i], 6% in HL	Median 4 (2–24+) mo[j]	35% overall	Median 4 (2–18) months	Four weekly doses.

HABA = human anti-bispecific antibody, HACA = human anti-chimeric antibody, HAMA = human anti-mouse antibody, HARA = human anti-ricin antibody, HL = Hodgkin's lymphoma, MR = minor response, NR = not reported, SD = stable disease and SCT = stem cell transplantation.

[a] Eight additional patients later treated; 4/12 responses [71].

[b] Two infusion schedules.

[c] Out of 15 evaluable patients, 14 having HL.

[d] One of four patients with stable disease was on prednisone.

[e] One disease stabilization lasted 12 months.

[f] The one minor response lasted 4 months.

[g] Data from final poster presentation.

[h] Out of 38.

[i] Four of six responding patients also received steroids.

[j] Median estimated from data.