Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Monoclonal antibody therapy for classical Hodgkin lymphoma

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Major advances in the treatment of B-cell lymphoma resulting from the introduction of a monoclonal antibody to the CD20 antigen 15 years ago have left Hodgkin lymphoma (HL) aside. This has changed with the success of the anti-CD30 antibody conjugated with an antitubulin agent, brentuximab vedotin, recently approved for the treatment of adult patients with relapsed or refractory CD30$^+$ HL following autologous stem cell transplantation (ASCT) or following at least two prior therapies when ASCT or for which multi-agent chemotherapy is not a treatment option. The magnitude of clinical activity of the new antibody has also prompted research on biologic functions of the CD30 molecule, as well as exploring other potential targets present on multinucleated Reed–Sternberg cells and the surrounding inflammatory area for a range of antibodies. This article will review the accumulating clinical data on the use of monoclonal antibodies in the treatment of classical HL with focus on CD20 and CD30 targets. We describe possible mechanisms of action, efficacy and toxicity related to administration of rituximab, brentuximab vedotin, daclizumab and other antibodies investigated in Phase I and II trials for classical HL.

Keywords: brentuximab vedotin • CD20 • CD25 • CD30 • daclizumab • Hodgkin lymphoma • monoclonal antibodies • rituximab

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The treatment of B-cell lymphoid malignancies was revolutionized 15 years ago by the advent of the monoclonal antibody to the CD20 antigen. The unprecedented success of this therapy was the result of a combination of a number of lucky choices and circumstances in the development of rituximab; the target antigen consistently present on the majority of lymphoma cells in the majority of B-cell lymphoma entities, the human-type Fc portion of the antibody being capable of effective engagement of the host cytotoxic cells and complement, the lack of immunogenicity of the product avoiding induction of neutralizing antibodies, the substantial anti-B-cell activity of the antibody when used either alone or in combination with chemotherapy, and the synergistic activity with chemotherapy without clinically significant additive toxicity. As shown by numerous randomized clinical trials and registry-based reports, rituximab significantly improved all aspects of disease control: response rate, remission duration, overall survival and quality of life in nearly all clinical conditions related to B-cell malignancy [1–3]. Hodgkin lymphoma (HL) was not included in this success story because when rituximab was developed, the CD20 antigen was not considered a reasonable target for this condition. This has changed recently with the growing evidence of a pathogenetic role of the tumor microenvironment in HL, including B-cell accumulation and a tumor-promoting function.

The category of HL involves two distinct disease variants: classical HL (cHL), which represents 95% of HL cases, and nodular lymphocyte-predominant HL (NLPHL). NLPHL is a very rare entity that has a different histopathology, immunophenotype

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and clinical outcome from cHL. This review specifically addressed the cHL variant. cHL is a monoclonal B-cell neoplasm composed of malignant mononuclear Hodgkin and multinucleated Reed–Sternberg cells (HRS) residing in a heterogenous mixture of non-neoplastic inflammatory and accessory cells. In cHL, malignant HRS cells represent less than 10% of the tumor cell infiltrate.

The latest advances in immunology showed the importance of the HRS microenvironment for disease outcome. The inflammatory tissue surrounding HRS cells is composed of lymphocytes, neutrophils, histiocytes, eosinophils, plasma cells, fibroblasts and collagen fibres. This complex microenvironment plays an essential role for HRS survival, and HRS cells stimulate the stroma formation by attracting cells with cyto/chemokines. HRS are derived from mature B cells of the germinal center that have lost the normal B-cell gene expression program. In rare cases, neoplastic cells are derived from peripheral, post-thymic T cells. The immunophenotype of HRS cells is characteristic of the expression of CD30 in nearly all cases and CD15 in a majority of cases. CD30 and CD15 are both expressed on the membrane and the Golgi area of the cytoplasm. CD20 may be expressed at variable intensity in 30–40% of cHL cases and only present on a minority of the neoplastic cells. The B-cell antigen CD79a is rarely present and the B-cell-specific activator protein PAX5/BSAP is expressed in 95% of cases. Although weaker than on reactive B cells, PAX5 expression reflects the B-cell nature of the HRS cells. CD45, CD75 and the macrophage specific PG-M1 epitope of the CD68, are consistently absent [4].

cHL accounts for up to 20% of all lymphomas and is highly curable with current chemotherapy and radiotherapy. Long-term survival for all patients is close to 80% and for those with initial limited disease stage, survival is even higher [5]. Relapses occur in approximately a quarter of cases. The most effective therapeutic option for eligible patients with chemosensitive relapse is a second-line therapy consolidated with autologous stem cell transplantation (ASCT), providing a 10-year survival of around 50% [6]. For non-ASCT eligible patients and those who relapse after ASCT, only chemotherapy of a palliative nature is available. Median survival is less than 3 years for these patients. Therefore, there is an unmet need for more efficacious and tolerable treatment methods for this group of patients (Table 1).

Rituximab (Rituxan™, MabThera™)

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the surface CD20 antigen. In cHL, it may directly eliminate a small percentage of malignant HRS cells expressing the CD20 antigen. As mentioned before, HRS cells express other specific receptors. TNF, CD30, CD40 and RANK support survival of malignant cells by activating NFκB nuclear factors, ERK kinases or Akt pathways and producing survival chemo/cytokines. Rituximab eliminates surrounding polyclonal cells carrying the CD20 antigen and ligands for these receptors are what leads to deprivation of HRS cells of survival signals. It is not clear whether the elimination of polyclonal B cells from the tumor mass is entirely suitable. B cells may also synthesize IL-10, which suppresses tumor growth and, therefore, using rituximab may decrease antitumor mechanisms of the immune system. This observation is based on *in vitro* and animal models and has to be validated in clinical trials. Recent studies also indicate that putative cHL stem cells carry memory B-cell phenotypes with the expression of surface Ig light chain, CD27, CD20 and aldehyde dehydrogenase (ALDH). These clonotypic $CD27^+/ALDH^+$ cells may be detected in the majority of cases only in peripheral blood of cHL patients but not in healthy donors. The elimination of $CD27^+/ALDH^+$ cells could prevent HRS cells from being sustained after chemotherapy and support rituximab therapy in cHL [7–9]. Further investigation is required in this area to confirm this hypothesis.

The pilot study exploring the utility of rituximab in cHL was performed by Younes in 2003 [10]. Eligible patients had recurrent or refractory cHL and had received a minimum of two prior treatment regimens including ASCT. Rituximab was administered weekly for six consecutive weeks, irrespective of CD20 expression on HRS cells. Objective responses were evaluated 3 weeks after the last dose of rituximab and every 3 months thereafter. A total of 22 patients were enrolled in the trial. The median number of prior treatments were four (range 2–12) and 82% of patients underwent ASCT. The response rate was 22%. One patient achieved a complete remission (CR). Median duration of response was 7.8 months (3.3–14.9 months). Remissions were observed in patients with lymph node and splenic but not extranodal disease, and were not related to CD20 expression on HRS cells. Moreover, B symptoms resolved in six out of the seven patients after completion of therapy. In two cases with a partial remission (PR), decline of the elevated serum IL-6 levels was found. The results of this trial suggested for the first time that eliminating non-neoplastic B-cells in cHL patients may lead to clinical responses including resolving of systemic B symptoms independently of CD20 expression on HRS cells [10]. In an attempt to enhance the therapeutic effect of rituximab, Yasuhiro performed a Phase II trial combining rituximab with gemcitabine [11]. A total of 33 patients with recurrent or refractory cHL were enrolled in the study. The median age (range) of patients was 32 (19–81) years, 55% of the patients had ASCT in the past. Rituximab was administered at the standard dose every week for six consecutive weeks in combination with

gemcitabine on days 1 and 8 of a 21-day cycle at a dose of 1250 mg/m^2. Objective response rate (ORR) was assessed after two cycles of treatment. The maximum number of cycles was four. A total of 82% of patients had no CD20 expression on HRS cells. ORR was 48% including CR in 15% of the cases. Unexpectedly, the median failure-free survival was generally short – 2.7 months (range: 0.9–18.3 months) [11]. Currently, a pilot Phase II study of rituximab, gemcitabine and vinorelbine combination for relapsed and refractory cHL is ongoing to evaluate activity and safety of this regimen in a similar group of patients. In addition, the study will determine the rate of adequate stem cell collection in patients eligible for stem cell transplantation [101].

An Italian group evaluated rituximab added to the salvage chemotherapy GIFOX before ASCT in refractory cHL. After three cycles of R-GIFOX in the group of 21 patients, ORR was 86% and 76% of patients achieved CR. In those patients who underwent ASCT (eight patients), the failure-free survival rate was 57% at 42 months of observation [12].

Rituximab was also evaluated in the first-line treatment of cHL. In a Phase II study, 85 treatment-naive, advanced-stage cHL patients received six doses of weekly rituximab starting with the first dose of ABVD chemotherapy. A total of 78 patients were evaluated; median age (range) was 32 (18–72) years, 50 patients (64%) were at stage III/IV of the disease, CD20 positivity was 18% (14 out of 70 cases). At a median follow up of 68 months (range: 26–110 months), 5-year event free survival (EFS) and overall survival (OS) for the whole group was 83 and 96%, respectively, and in patients with clinical stage III/IV, EFS was 82%. The 5-year EFS in patients with CD20 positivity was 93% compared with 77% in patients without CD20 expression. These differences were not statistically significant (p = 0.23). Reported adverse events of grade 3/4 included neutropenia in 18 patients (23%), fatigue in seven cases (9%) and nausea in six cases (8%). One patient discontinued treatment after the fifth cycle due to prolonged cytopenia. One patient developed *Pneumocystis jirovecii* pneumonia after the third cycle [13].

The main goal of the Kasamon study was to explore the biologic effects of rituximab in correlative laboratory studies in new diagnosed cHL patients [14]. Secondary objectives included the evaluation of clinical outcomes. A total of 49 patients were enrolled to the study; 69% of them had stage IIB–IV of the disease and 8% had CD20$^+$ HRS cells. Rituximab was administered on days: -7, 1, 8, 15 and 22 of cycle one and days 1 of cycles two, four and six of ABVD regiment. After six cycles, 39 patients (81%) achieved CR, 7 patients (15%) PR and one patient had stable disease. There were two progressive diseases. Radiation therapy was performed in only 8% of cases. The 42 patients without progression were alive and in continued remission with a median follow up of 33 months (11–56 months). The 3-year EFS and OS rates were 83 and 98%, respectively. The treatment was generally well tolerated with the possible exception of increased infection risk. Laboratory studies revealed that 21 out of 24 (88%) patients had detectable clonotypic CD27$^+$/ALDH$^+$ cells at baseline After treatment completion they were detectable only in two cases. Although CD27$^+$/ALDH$^+$ cells re-emerged in the blood of three patients, at follow up, patients still remain in disease remission. In general, survival of clonotypic B-cells in the blood was associated with a greater relapse incidence. In the study, authors also investigated the incidence of Epstein–Barr Virus (EBV) in HRS cells, which is previously shown, can be negative prognostic factors for the disease outcome. In the study, incidence of EBV-DNA at baseline was correlated with higher disease activity, and expression of CD68$^+$ macrophages. Also, EBV-DNA copy numbers decreased during treatment [14–16].

Data from these Phase II studies suggested that rituximab in combination with standard first-line treatment may possibly improve ORR and OS rates in cHL; however, it has to be confirmed in randomized Phase III trials with sufficient follow up. Clinical trials exploring the usefulness of rituximab in combination with front line therapies are currently ongoing [102–104]. **Table 2** summarizes rituximab clinical trials that were conducted in cHL patients.

Table 1. Monoclonal antibodies in the treatment of classical Hodgkin lymphoma.

Antibody	Target	Target	Phase	ORR/CR (%)	Ref.
Brentuximab vedotin	CD30	HRS cells	II	75/34	[36]
Daclizumab	CD25	HRS cells	I/II	63/40	[44]
Lucatumumab	CD40	HRS cells	I/II	NA	[107]
Bevacizumab	Anti-VEGF	HRS cells	II	NA	[110]
Rituximab	CD20	B cells	II	22/4	[10]
Alemtuzumab	CD52	T cells	II	NA	[109]

CR: Complete response rate; HRS: Hodgkin and multinucleated Reed–Sternberg; ORR: Objective response rate.

Brentuximab vedotin (SGN-35, Adcetris™)

The CD30 molecule is a member of the TNF receptor family [17]. It is present in a variety of cells including activated T, B and NK cells or a number of malignant cells including embryonal or nasopharyngeal cancers [18–22]. CD30 is expressed in the majority of cases of systemic mastocytosis, and in approximately 20–30% of diffuse large B-cell lymphomas (not otherwise specified) [23,24]. More than 90% of HRS cells express CD30 in cHL. CD30 can be bound to the surface of the cell, be present in the Golgi area of the cytoplasm or released to the serum

Table 2. Clinical studies of rituximab in classical Hodgkin lymphoma.

Author (year)	Disease status	Therapy	Patients (n)	ORR/CR (%)	Outcome	Ref.
Younges *et al.* (2003)	Relapsed/refractory	Rituximab	22	22/4	Median response duration 7 months (3.3–14.9)	[10]
Yasuhiro *et al.* (2008)	Relapsed/refractory	Rituximab/ gemcytabine	33	48/15	Median response duration 2.7 months (0.9–18.3)	[11]
Corazzelli *et al.* (2009)	Relapsed/refractory	Rituximab/GIFOX	21	86/76	Median response duration for CR patients: 12 months	[12]
Younges *et al.* (2012)	Naive	Rituximab/ABVD	78	92/87	5-year EFS: 83% 5-year OS: 93%	[13]
Kasamon *et al.* (2012)	Naive	Rituximab/ABVD	49	96/81	3-year EFS: 83% 3-year OS: 98%	[14]

CR: Complete remission; EFS: Event-free survival; ORR: Objective response rate; OS: Overall survival.

(soluble form). Elevated levels of soluble CD30 at the diagnosis in cHL patients are correlated with tumor burden and poor outcome [25]. In cHL, CD30 promotes HRS survival and growth. The CD30 ligand enhances IL-6, TNF-α and ICAM-1 production. It promotes NF-κB transcription factor, which regulates synthesis of various cytokines (IL2, IL6, IL8, IL12, G-CSF and GM-CSF) and induces expression of multiple anti-apoptotic genes that promote HRS survival. Additionally, CD30 activation on T and B cells enhances production of IL-5, INF-γ and immunoglobulins in surrounding reactive cells that support the durability of HRS [19]. Under certain circumstances, NF-κB activation can induce various degrees of proliferation in HRS and accompanying cells based on *in vitro* observations [26]. After allotransplatation, the inhibition of the CD30 intracellular signaling pathway diminishes the donor alloreactive $CD4^+$ T-cell migration to the GI tract and can prevent $CD4^+$ T-cell-mediated graft-versus-host disease (GVHD) in internal organs [27].

The CD30 antigen has been thought to be a promising therapeutic target since the 1990s when Falini *et al.* investigated the ability of the Ber-H2 (CD30) monoclonal antibody to target *in vivo* HRS cells [28]. Six patients were recruited to the study and injected with Ber-H2 mixed with ^{131}I-labelled Ber-H2. The activity of Ber-H2 was evaluated by immunohistological staining of tumor biopsies and immunoscintigraphy [28]. The first and second generations of naked anti-CD30 antibodies (cAC10, MDX-060, MDX-1401 and XmAb2513) presented high activity *in vitro*. However, they had poor antigen-binding ability and lost their activity mediated by the immune effector cells *in vivo* [29–32]. To increase their therapeutic effect, the Cancer and Leukemia Group B conducted a randomized, double-blind Phase II trial of the first-generation SGN30 antibody combined with gemcitabine, vinorelbine and liposomal doxorubicin in relapsed cHL patients. After recruiting 30 patients, the trial was closed due to substantial pulmonary adverse events, including fatal pneumonia. There was also no improvement in ORR and EFS [33]. The other attempt to enhance antitumor activity was the conjugation of the antibody to active particles: RNases and radioisotopes. Phase I trials did not show any clinical activities with such combinations [34].

Until now, therapeutic activity was only proven with the anti-CD30 antibody–toxin combination. An example of a successful combination is the antibody–drug conjugate brentuximab vedotin (SGN35, Adcetris™). It is composed of first-generation human chimeric immunoglobulin G1 anti-CD30 antibody (cAD10) conjugated by the peptide linker to monomethyl auristatin E (MMAE), the synthetic analog of the antitubulin agent, dolastatin 10. The antibody is produced in hamster ovary cells. Each particle of antibody is attached to four molecules of MMAE. After intravenous infusion, the maximum concentration of the drug is observed in 30 min and the estimated terminal half-life is 4–6 days. It achieves a steady concentration within 21 days of administration. Approximately 68–82% of MMAE are bound plasma proteins, a small portion undergoes metabolic processing via cytochrome P450, but the majority is eliminated unchanged in the feces. SGN35's mechanism of action is to combine inhibiting CD30 intracellular signaling and microtubule destabilization. SGN35 binds to the CD30 surface antigen, suppressing cytokine synthesis and the TNF signal pathway. It then undergoes endocytosis and moves into the lysosomes. There, MMAE is cleaved from cAC10 by enzymatic processes and disrupts the microtubule network, leading to G2/M cell arrest and apoptosis. The antitumor activity of SGN35 with a tolerable toxicity profile was demonstrated *in vitro* and *in vivo* animal studies with rats and monkeys [35,36].

The first clinical results of a multicenter, dose-escalation, open-label Phase I study were published by Younes *et al.* in 2010 [37]. The trial was conducted in 45 patients with $CD30^+$ relapsed or refractory lymphomas, 42 of

whom were cHL. The median age of patients was 36 (range 20–70) years, the median number of previous chemotherapy regimens was three (range 1–7), and 33 patients (77%) had ASCT. SGN35 was administered at the dose of 0.1–3.6 per kg of body weight, every 3 weeks up to 14 doses. The maximum-tolerated dose was 1.8 per kg. The most common adverse events, mainly grade 1 or 2, were fatigue, pyrexia, diarrhea, nausea, neutropenia and peripheral neuropathy. The dose-limiting toxicities were febrile neutropenia, prostatitis and hyperglycemia. One patient treated at a dose of 3.6 mg/kg experienced fatal outcome due to febrile neutropenia and sepsis. Objective responses were noted in 17 patients; including 11 CR. ORR in the group receiving 1.8 mg/kg was 50%. Median response duration was 9.7 months [37]. Fanale *et al.* conducted another Phase I, dose-escalation study of brentuximab vedotin given once a week (days: 1, 8 and 15 of a 28-day cycle) [38]. The aim of the study was to assess whether weekly administration of the drug could improve antitumor activity. A total of 44 patients with $CD30^+$ relapsed/refractory lymphomas were enrolled, 38 of whom were HL. The median patient age was 33 (range 12–82), the median number of previous chemotherapy regiments was three (range 1–8) and 30 patients (68%) had ASCT. SGN35 was given at the dose of 0.4–1.8 mg per kg of body weight. The maximum tolerated dose was 1.2 mg/kg. ORR was 59% (n = 24), with 34% (n = 14) CR. Median follow up was 45.1 weeks (range 6–91), median progression-free survival: 28.7 weeks (range 7.3–83.6) and OS was not reached during the time of observation. The most common adverse events were peripheral sensory neuropathy, fatigue, nausea, diarrhea, arthralgia and pyrexia; and the majority of events were mild-to-moderate in severity [38].

A pivotal multicenter, Phase II trial opened recruitment in 2009. A total of 102 patients with relapsed or refractory cHL, after ASCT, received 1.8 mg/kg of brentuximab vedotin intravenously every 3 weeks for up to 16 cycles (median 9, range: 1–16). The median age of the patients was 31 years (range: 15–77), and 71% had primary refractory disease with a median number of prior chemotherapies of 3.5 (range: 1–13). Median time to relapse after ASCT was 6.7 months (range: 0–131). The ORR was reported in 73% of cases, 33% achieved CR and 40% PR. The median PFS was 5.6 months. The median duration of response for patients who achieved CR was 20.5 months. 30% of patients were alive and free of relapse after 18.5 months of observation. The most common treatment-related adverse events were: peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%), neutropenia (19%) and diarrhea (18%). A total of 56% experienced grade 3 or higher adverse events. There were no deaths related to the study drug within 30 days of the last SGN35 administration [39].

Recently, Chen *et al.* presented long-term survival data of the abovementioned NCT00848926, Phase II study of brentuximab vedotin in patients with relapsed and refractory cHL [39,40]. In a cohort of 102 patients ORR was 75% (76 patients), with 33% CR (34 of cases). At the time of analysis, the median duration of observation was 29.5 months (range: 1.8–36.9), median OS for the whole group and for the patients who obtained CR was not reached. Median OS for the group of patients who achieved PR was 31.6 months and for SD 20.6 months. No significant difference in OS was obvious in patients who had relapsed above 1 year or within a year after ASCT. Treatment-related adverse events were similar to those described before [40].

More frequent adverse events including fatigue and sensory neuropathy were reported in the older patient population. Other toxicity profiles and clinical responses were consistent with those observed in the Phase II studies of younger patients [41].

Brentuximab vedotin was approved in the USA in October 2011. In August 2012, it was approved in Europe for the treatment of adult patients with relapsed or refractory $CD30^+$ HL following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. It was also approved for the treatment of adult patients with relapsed or refractory systemic anaplastic large-cell lymphoma.

Brentuximab vedotin was also tested earlier in the disease course. Interim results presented at American Society of Hematology (ASH) 2012 meeting demonstrated that SGN35 in a second-line salvage monotherapy resulted in an ORR of 80% and CR of 50% with acceptable toxicity and without adverse impact on stem cell collection or post-ASCT engraftment [42].

In the previous studies, the dose of 1.8 mg/kg SGN35 was used [39] and the length of treatment did not exceed 16 applications of the drug at 3-week intervals. In view of the encouraging results, there are attempts to extend the time of treatment or to increase frequency of administration of brentuximab vedotin in heavily pretreated patients. Preliminary results of prolonged therapy were presented by Forero-Torres recently [43]. A total of 15 patients with relapsed/refractory disease (ten with cHL and five with ALCL) received more than 16 consecutive cycles of brentuximab vedotin monotherapy with a comparable safety profile [43]. Fanale *et al.* conducted a Phase I dose-escalation trial that evaluated a schedule of a 28-day cycle of brentuximab vedotin administered on days 1, 8 and 15 [38]. The starting dose of 0.4 mg/kg was escalated to 1.4 mg/kg or until a dose-limiting toxicity occurred. At the time of analysis, ORR in 41 patients was 59% with 34% CR; median duration of response was not reached after 45 weeks of follow-up and median PFS was 28.7 weeks (range 6–91). The profile and intensity

of adverse events did not differ from that described in previous trials [38].

Bartlett *et al.* conducted a Phase II study to investigate if retreatment with brentuximab vedotin can induce remissions in a heavily pretreated population of CD30$^+$ lymphomas [44]. Patients with relapsed/refractory cHL (14 patients) and ALCL (eight patients) who achieved objective responses with prior SGN35 therapy and relapsed after discontinuing therapy were eligible for the study. At interim analysis, objective responses were observed in 13 out of 20 evaluated patients (65%). Among patients with cHL, CR was achieved in three, PR in five, SD in three and three patients had a PD. The median duration of response to retreatment was 10.8 months and for the patients who achieved CR, the median response duration was not reached. The toxicity was manageable but in three of the 11 patients who had pre-existing peripheral neuropathy, it worsened with treatment [44].

Brentuximab vedotin therapy results in high response rates that are, however, not of unlimited duration, as demonstrated by clinical trials. Thus, for patients with a disease recurrent after cell transplant, allogeneic stem cell transplantation is still the only potential curative option. SGN35 selectively targets CD30 lymphoma cells and the host polyclonal immune system cells settled in the tumor mass. This might enhance a graft versus lymphoma response and modify GVHD by the induction of immunogenic cell death activating HL-specific TH17-like phenotype T cells [45]. Chen *et al.* retrospectively investigated the records of 18 patients with cHL treated with brentuximab vedotin prior to reduced-intensity allogeneic hematopoietic cell transplantation (allo-RIC) [46]. All the patients had refractory/relapsed cHL and a history of ASCT. Six patients were in CR and eight in PR prior to allogeneic hematopoietic cell transplantation. The engraftment time, transplant toxicity and incidence of acute (28%) and chronic (56%) GVHD were as expected. There was no increased evidence of cytomegalovirus/EBV infections. The 1-year OS was 100% and the PFS was 92.3%, giving hope that treatment with brentuximab vedotin prior to allotransplant can help provide significant disease control in this group of patients [46].

Recently, Gibb and colleagues published their experience with SGN35 therapy before allo-RIC in patients enrolled into the Named Patient Programme during 2010–2011 in a single Cancer Centre in the UK [47]. Patients received a median of 5.5 cycles of brentuximab vedotin. Median PFS for the whole group (18 cHL, five anaplastic lymphoma and one T-cell lymphoma) was 5.1 months and for patients with CR, PFS was not achieved in 12.9 months of follow-up. For cHL patients, ORR was 72% with a CR of 17%. The best responses were seen after four doses of brentuximab vedotin. Six patients with cHL underwent allo-RIC as of April 2012. According to the report, allo-RIC should be scheduled early, in accordance with the best present response [47].

In a study by Gopal *et al.*, brentuximab vedotin was administered to 25 cHL patients after allotransplatation [48]. These patients were more than 100 days post-allotransplantation (median 46 months) and had no active GVHD. A total of 19 patients had disease progression at the time of trial enrollment. Patients received a median of eight doses of brentuximab vedotin (range 1–16). ORR was 50% with 38% of patients with CR, PFS 7.8 months and median OS was not reached in 13 months of observation. Peripheral sensory neuropathy (48%), nausea (28%), alopecia (24%), neutropenia (24%), fatigue (20%) and vomiting (20%) were most commonly reported as related to the study drug. Resolution or improvement of the polineuropathy was reported in 54% of cases during the study [48]. Similar results were presented at the 2011 ASH Meeting by Illidge *et al.* [49]. These results suggest that brentuximab vedotin treatment can be safely used in a selected group of patients after allotransplantation but further studies in larger groups of patients are needed.

Although a synergistic effects of SGN35 with chemotherapy were suggested from preclinical studies, the interactions of brentuximab vedotin with cytotoxic agents, in particular with vinorelbine or other vinca-alkaloid derivatives, were not evident and require more investigation. For this reason, a number of new clinical trials are currently ongoing, including studies in newly diagnosed cHL, in first relapse and as a salvage before SCT. The results of the Phase I study with newly diagnosed cHL patients treated with front-line therapy was presented at the ASH Meeting in 2012 by Ansell [50]. The primary goal of the trial was to evaluate the incidence of adverse events, laboratory abnormalities and the safety of brentuximab vedotin at dosing up to 1.2 mg/kg combined with chemotherapy: ABVD or AVD according to cohort assignment. In 51 patients, no dose-limiting toxicity was observed with either regimen.

Approximately 40% of patients experienced adverse events. They were reported in both the ABVD and AVD cohorts, respectively; nausea (76 vs 77%), neutropenia (80 vs 69%), peripheral sensory neuropathy (72 vs 65%), vomiting (60 vs 38%), fatigue (44 vs 46%) and constipation (48 vs 31%). In the ABVD cohort, 11 out of 25 (44%) patients had pulmonary toxicity, interstitial lung disease or pneumonitis that led to discontinuation of bleomycin and in two cases, to death. After these events the ABVD arm was discontinued due to toxicity. Combination of brentuximab vedotin with a bleomycin-containing regimen is not recommended. Out of 11 ABVD arm patients, seven completed treatment with AVD and brentuximab vedotin. No pulmonary toxicity was observed in the AVD cohort. The frequency of neuropathy was

similar in the ABVD (72%) and AVD (73%) arms. In total, 95% of patients in the ABVD cohort and 92% in the AVD achieved CR at the end of front-line therapy [50].

Recently, the US FDA published drug safety communication due to the incidence of a few cases of progressive multifocal leukoencephalopathy after treatment with brentuximab vedotin and an increased risk of pulmonary toxicity after a combination of brentuximab vedotin with bleomycin [105]. Other serious events include: Stevens–Johnson syndrome and tumor lysis syndrome. Published and currently ongoing clinical trials of brentuximab vedotin in cHL are listed in Tables 3 & 4.

Other monoclonal antibodies used in the treatment of cHL

A high percentage of HRS express CD25 antigen, the alpha chain of the IL-2 receptor. CD25 is also present on the surface of other lymphoid malignances and tumor-infiltrating $CD4^+$ T cells such as T-regulatory cells (T regs). CD25 is not present on regular resting lymphoid cells. A high level of IL-2 encourages tumor and infiltrating polyclonal cell growth, plays a role in either enhancing the antitumor host response or in tumor survival [51,52]. $CD4^+/CD25^+$ T regs express CTLA4 and synthesize IL-10, both of which sustain HRS growth and the proficiency of T regs.

Daclizumab is a humanized monoclonal antibody of IgG1 that binds CD25. It was approved by the FDA in 1997 as an immunosuppressive drug for use in kidney transplantation. It is currently under clinical investigation for lymphoid malignances, including cHL. Due to disappointing efficacy of the anti-CD25 monoclonal antibody alone or conjugated to the *Pseudomonas aeruginosa* toxin PE38, daclizumab was armed with a radioactive Yttrium-90 (Y90) [53]. In a trial conducted by O'Mahony *et al.*, patients with refractory cutaneous T-cell lymphoma, two patients with peripheral T-cell lymphoma, two with ALCL and ten patients with cHL were treated with daclizumab [54]. The patients' median age was 54 years (range: 24–75) and all had refractory disease with a median of four prior therapies (range: 1–10). They received Y90-daclizumab every 6–10 weeks, and overall 38 cycles were administered with the median of 1 cycle (1–6). ORs have only been seen in cHL: two patients with CR, two patients with PR [55]. Recently, there have been encouraging results with the humanized form of Y90 daclizumab in the treatment of patients with cHL. A total of 30 refractory cHL patients were evaluated in the trial by Waldmann *et al.* [54]. A total of 98 cycles of treatment were administered with a median radiation dose of 40 mCi. After completing treatment, seven patients achieved PR and 12 patients CR. Toxicities were transient; bone marrow suppression and myelodysplastic syndrome in three cases. Responses were also reported for the five patients with CD25-negative HRS and were probably due to the antibody reacting with the $CD25^+$ T regs [54].

It appears that daclizumab coniugated with radioactive Y90 can be considered as a therapeutic option for selected cHL patients. Thus, two ongoing clinical trials are exploring the activity of daclizumab alone or in combination with high-dose chemotherapy and ASCT in this set of patients [106,107].

Table 3. Clinical studies of brentuximab vedotin in classical Hodgkin lymphoma.

Author (year)	Status of cHL	Therapy	Patients (n)	ORR/CR (%)	Outcome	Ref.
Younes *et al.* (2010)	Relapsed/ refractory†	Brentuximab vedotin	42	36/21	Median response duration 9.7 months	[37]
Fanale *et al.* (2012)	Relapsed/ refractory†	Brentuximab vedotin	44	59/34	Median PFS: 28.7 weeks	[38]
Younes *et al.* (2012)	Relapsed/ refractory	Brentuximab vedotin	102	75/34	Median response duration 5.6 (5–9) months	[39]
Chen *et al.* (2012)	Relapsed/ refractory	Brentuximab vedotin	102	75/33	Median OS not reached at the 29.5 months (1.8–36.9) observation	[40]
Bartlett *et al.* (2012)	Relapsed/ refractory	Brentuximab vedotin – retreatment	14	57/21	Median response duration 10.8 months	[44]
Gopal *et al.* (2012)	Relapsed/ refractory after allo-HCT	Brentuximab vedotin	25	50/38	PFS 7.8 (0.5–12.5) months OS not reached in 13 months of observation	[48]
Ansell *et al.* (2011)	Naive	Brentuximab vedotin/ABVD	31	Ongoing	Ongoing	[50]

†Data of cHL patients, Phase I, dose-escalating study.

allo-HCT: Allogeneic hematopoietic cell transplantation; cHL: Classical Hodgkin's lymphoma; CR: Complete response; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival.

Table 4. Current clinical trials with brentuximab vedotin for classical Hodgkin lymphoma.

Indication	Drug combination	Phase	Identifier	Ref.
Newly diagnosed, stage I/II	ABVD followed by brentuximab vedotin	Pilot	NCT01578967	[112]
Newly diagnosed, stage I/II	Brentuximab vedotin + AVD	II	NCT01534078	[113]
Newly diagnosed, unfavorable, I/II stage	Brentuximab vedotin + AVD + involved-site radiotherapy	Pilot	NCT01868451	[114]
Newly diagnosed, above 60 years old	Brentuximab vedotin	II	NCT01716806	[115]
Newly diagnosed, above 60 years old	Brentuximab vedotin + AVD	II	NCT01476410	[116]
Newly diagnosed, advanced stage	Brentuximab vedotin + ABVD	III	NCT01712490	[117]
Newly diagnosed, advanced stage	Brentuximab vedotin + BEACOPP	II	NCT01569204	[118]
Newly diagnosed, HIV positive	Brentuximab vedotin + AVD	I/II	NCT01771107	[119]
Relapsed or refractory	Brentuximab vedotin	II	NCT01393717	[120]
Relapsed or refractory	Brentuximab vedotin + bendamustine	I/II	NCT01657331	[121]
Relapsed or refractory	Brentuximab vedotin + rituximab	Pilot	NCT01900496[†]	[122]
Relapsed or refractory	Brentuximab vedotin + gemcitabine	I/II	NCT01780662	[123]
Relapsed or refractory	Brentuximab vedotin + temsirolimus	I	NCT01902160	[124]
Relapsed or refractory	Brentuximab vedotin + bendamustine	I/II	NCT01874054	[125]
Relapsed or refractory	Brentuximab vedotin + ipilimumab	I	NCT01896999[†]	[126]
Relapsed or refractory	Brentuximab vedotin + gemcitabine, vinorelbine, pegylated liposomal doxorubicin	II	NCT00337194[‡]	[127]
Relapsed or refractory, eligible for ASCT	Brentuximab vedotin	II	NCT01508312	[128]
Relapsed or refractory	Brentuximab vedotin maintenance after ASCT	III	NCT01100502[‡]	[129]

[†]Not yet recruiting; [‡]Completed.
ASCT: Autologous stem cell transplantation.

The CD40 antigen belongs to the TNF receptor family. It is detected both on HRS and on microenvironment cells. It is also commonly expressed on the surface of mature B cells and B-cell malignances such as indolent, aggressive non-HLs and multiple myelomas. CD40 is involved in direct signal transduction, interfering with the NF-κB transcription factor and recruiting the host immune system in the mechanism of antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis.

Two humanized anti-CD40 monoclonal antibodies are currently under clinical investigation in cHL. SGN-40 (dacetuzumab) is accepted for Phase II clinical trials in diffuse large B-cell lymphoma, chronic leukocytic leukemia and multiple myeloma. Currently, there are no data about its activity in cHL. Lucatumumab (HCD122) is a fully human antagonistic anti-CD40 monoclonal antibody that inhibits the connection between CD40 and its ligands mediating ADCC. A Phase I/II study in relapsed cHL is currently ongoing [108].

Theoretically, CD80 could also serve as another attractive target for immunotherapy of cHL. Galiximab (anti-CD80 monoclonal antibody) is a humanized IgG1 monoclonal antibody directed against CD80, which is the natural ligand for the T-cell antigen CD28 and mediates T- and B-cell adhesion. Its mechanism of action involves inhibition of the NF-κB intracellular pathway, up-regulating proapoptotic molecules and enhancing ADCC. There is no indication for the efficacy of galiximab in cHL yet, but it demonstrates modest antitumor activity in follicullar lymphoma [56,57]. Several clinical trials in non-HL are currently ongoing [109].

The CD52 antigen is expressed on the surface of mature lymphocytes B, T, NK, monocytes, dendritic cells, mast cells, fibroblasts and eosinophils but not by granulocytes, red blood cells, platelets, hematopoietic progenitors and HRS. The effect of CD52 signaling is not completely understood. It may be involved in cell migration and co-stimulation. If the reactive cells of the cHL microenvironment support the survival of HRS, their elimination can be of clinical benefit making CD52 a promising target for monoclonal antibody therapy. Alemtuzumab is a recombinant DNA-derived humanized monoclonal anti-CD52 antibody that is directed against cell surface glycoprotein, and may target inflammatory cells in the cHL microenviroment. A combination of alemtuzumab and dose-adjusted EPOCH + rituximab is currently being tested in a clinical trial in relapsed/refractory cHL patients (NCT01030900) [110].

As assessed by immunohistochemical staining, HRS expresses VEGF receptors in the majority of cases [58]. VEGF stimulates the growth of blood vessels in the tumor, supporting tumor development. There are a few reports demonstrating that cHL patients with high levels of VEGF have a shorter survival. This indicates that anit-angiogenic treatment may be of merit in cHL.

Bevacizumab vedotin is a widely explored drug in many indications, mostly in solid tumors. It is a humanized monoclonal antibody that inhibits VEGF-A. In preclinical studies, bevacizumab delays the growth of HL tumors in immune-deficient mice [59]. A clinical trial of bevacizumab combined with ABVD regimen in newly diagnosed advanced-stage cHL was initiated in 2008. Despite active status, the study is not recruiting new participants so the date of completion of enrolment is currently unknown [111].

Future perspective

After decades of stagnation in development of novel agents for HL, there is a number of new compounds emerging from the recent clinical studies that may change treatment paradigms. These include monoclonal antibodies, histone deacetylase inhibitors, mTOR inhibitors and immunomodulating agents.

Monoclonal antibodies, like brentuximab vedotin and rituximab, already demonstrated efficacy in cHL [12,40] and are quite close to entering clinical practice. A combination of rituximab with ABVD chemotherapy in first-line treatment leads to excellent responses in advanced cHL – ORR/CR rates above 90 and 85% [13,14]. Brentuximab vedotin alone can produce CR rates close to 40% and the same PR rate in refractory cHL [39,40]. Monoclonal antibody therapy is in general exceptionally well tolerated. Rituximab added to chemotherapy does not increase toxicity. Brentuximab vedotin can cause temporary, moderate peripheral neuropathy in approximately 50% of patients and bone marrow suppression in 20% of cases, but with careful use, can be safety administered. Although the ultimate role of these agents in cHL requires further randomized Phase III trials with a sufficient follow up, brentuximab vedotin was recently approved for refractory cHL based on the excellent ORR in the Phase II trial [105]. Rituximab is still experimental, but Phase III trials in front-line therapy are ongoing [102–104]. Daclizumab is another monoclonal antibody under clinical investigation. Administration of daclizumab conjugated with a radioactive Y90 resulted in an ORR of 63% and a CR of 40% as presented at ASH 2012 [54]. Other antibodies targeting HRS cells or tumor microenvironment are also under investigation. Further improvements of immunotherapy in cHL will likely involve the antibody in first-line treatment so that curability of patients could be improved upfront. Identifying predictive markers will be of particular value. For instance, external membrane exposure of antigen on the target cell can be a critical condition for the interaction with the ligand and possibly, a predictive factor for response to antibodies. Brentuximab vedotin and rituximab target different cellular compartments in cHL and a combination of these biological agents may be a reasonable research possibility.

Immunotherapy of HL with the monoclonal antibodies is currently widely entering clinical research and beginning to enter clinical practice as well. This holds a promise of further improving patient outcome by limiting refractory disease and possibly by decreasing toxicity of emerging combination treatments.

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Executive summary

Rituximab (Rituxan™, MabThera™)

- Combination of rituximab with ABVD chemotherapy is well tolerated and active in the front line therapy of advanced stages of classical Hodgkin lymphoma (HL).

Brentuximab vedotin (SGN-35, Adcetris™)

- Brentuximab vedotin monotherapy results in a substantial rate of objective responses including complete remissions in multiple-relapsed and treatment-refractory HL patients.
- Toxicity related to brentuximab vedotin is generally tolerable and manageable with a careful use.
- A proper place of brentuximab vedotin in a treatment algorithm of HL is a subject of a number of clinical trials.

Other monoclonal antibodies used in the treatment of classical Hodgkin lymphoma

- Radioimmunotherapy with Yttrium-90 daclizumab is a promising new method of systemic radiotherapy of relapsed/refractory classical HL.
- Other monoclonal antibodies for classical HL are under development.

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