The new therapeutical scenario of Hodgkin lymphoma

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Key Message: "In this review, we present the current standards of care for patients with classical Hodgkin lymphoma and outline some future directions for the development of new drug combinations for patients with both untreated as well as relapsed disease. We report the design and results of two trials that have recently evaluated a PET adapted strategy in the treatment of stage I-II disease and cover more extensively the results obtained with brentuximab vedotin and how this agent could be incorporated in the future in the standard of care for patients with advanced disease or patients who relapse after chemotherapy. Finally we describe the excellent results recently reported with two monoclonal antibodies targeting PD1 and results obtained with HDAC inhibitors in combination with chemotherapy or targeted agents. To our view, the possibility to adapt treatment strategies based on PET response and the incorporation of novel highly active agents into the standard of care, represent the challenge of the future to further improve treatment outcomes in patients with Hodgkin lymphoma."
Abstract

Hodgkin lymphoma (HL) remains one of the most curable human cancers, as modern combination chemotherapy and radiation therapy cure approximately 80% of patients. Over the last two decades, the major efforts were focused on the development of more intensive front-line regimens for patients with advanced stage HL, decreasing the number of chemotherapy cycles and radiation therapy field and doses for patients with early stage HL and incorporating positron emission tomography (PET) imaging in diagnostic, prognostic, and treatment planning. More recently, the improved knowledge of the molecular biology of the disease led to the development of highly active new agents, including the antibody-drug-conjugate brentuximab vedotin and immune checkpoint inhibitors. Accordingly, the current efforts are focusing on incorporating these new agents into standard of care regimens, aiming at further improving cure rates, while reducing treatment-related toxicity. In this review, we will focus on the current status of HL therapy and how the development of new agents is re-shaping standard of care regimens.

Keywords: Hodgkin lymphoma, PET response adapted therapy, Brentuximab Vedotin, Immune checkpoint inhibitors, HDAC inhibitors, New treatment combinations
Introduction

Hodgkin lymphoma (HL) is an uncommon B-cell lymphoma that accounts for approximately 10% of all lymphomas. The annual incidence in the US and in the EU is 2-3 new cases/100,000 (8,000 new cases/year in the US). In industrialized countries the majority of Hodgkin lymphomas are diagnosed in their late 20s/early 30s of age, with a second smaller peak in adults older than 55 years [1, 2]. The World Health Organization (WHO) classification recognizes two main HL types: nodular lymphocyte-predominant HL (NLPHL) and classical HL (cHL) which is further divided in four subtypes: nodular sclerosis cHL (NSCHL), mixed cellularity cHL (MCCHL), lymphocyte-depleted cHL (LDCHL) and lymphocyte-rich cHL (LRCHL) [3]. Classical HL accounts for 95% and NLPHL accounts for 5% of all HL. This review will focus on the treatment of cHL (hereafter, HL).

Histologically HL consists of mononuclear Hodgkin cells and multinucleated Reed-Stemberg (HRS) cells residing among an overwhelming number of reactive inflammatory cells (T cells, B cells, histiocytes, eosinophils, plasma cells, fibroblasts) and collagen fibres. Although the malignant HRS cells of HL are of B-cell origin, they infrequently express B-cell genes, including CD20 antigen and the B cell transcription factors OCT2, BOB1, and PU.1, presumably due to epigenetic reprogramming [4-6]. In the Western World, HRS cells are infected with the Epstein-Barr virus (EBV) in approximately 40% of HL patients, and in 100% of HL patients who are infected with the human immunodeficiency virus (HIV). HRS cells characteristically express CD30 surface receptors, a member of the tumor necrosis factor (TNF) receptor super family, that is expressed as a trans-membrane protein [7, 8]. The cytoplasmic tail contains several TNF receptor-associated-factor (TRAF)-binding sequences that mediate diverse signaling pathways, including activation of nuclear factor kappa-B (NF-kB) [9, 10]. CD30 ligand (CD30L, CD153), a member of the TNF superfamily, is expressed by both resting and activated B cells, activated T lymphocytes, monocytes, granulocytes, and natural-killer cells [11-13]. The exact physiologic function of CD30/CD30L in healthy
individuals is poorly understood, as no human diseases have been linked with CD30 or CD30L genetic alterations. In mice, CD30 may play a role in thymocyte negative selection, [14, 15] and self-tolerance [16-23].

It is remarkable to note that the high cure rate of HL was achieved by the development of empiric combination regimens, long before the cell of origin was identified [24]. Today, 80% of patients can be cured with modern therapy. Unfortunately, many cured patients do not live the expected life span, due to delayed treatment-related toxicity, including second malignancies and cardiovascular diseases [25]. Accordingly, the current treatment strategies are focusing on further improving treatment efficacy, while reducing treatment-related toxicity. These two strategies were addressed over the past two decades by developing more intensive front-line regimens for patients with advanced stage HL, and by decreasing the number of chemotherapy cycles and radiation therapy field and doses, for patients with early stage disease. More recently, PET imaging is used to develop response adapted treatment programs. As more novel, highly effective agents, are being identified, the current efforts are shifting to focus on rapidly incorporating these new agents into standard regimens. In this review, we will focus on the current status of HL therapy and how the development of new agents is re-shaping standard of care regimens.

**Early stage HL**

The treatment of patients with HL is based on the stage of the disease and the presence of adverse prognostic factors (Figure-1). Two widely used prognostic factor criteria classify patients into early favourable and early unfavourable groups (Table-1). Patients with any of these risk factors would be classified as having early unfavourable stage HL and those with no risk factors are considered as having early favourable stage HL [2]. Patients with early favourable disease are typically treated with 2 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) followed by 20 Gy involved field radiation therapy (IFRT) [26]. Recently, the international lymphoma radiology oncology group (ILROG) suggested using an
involved-site radiation therapy (ISRT) instead of the traditional involved field approach, however this strategy has not been studied in randomized trials [27]. Patients with unfavourable early stage disease are treated with 4 cycles of ABVD followed by 30 Gy IFRT. A recent randomized trial compared a more aggressive chemotherapy regimen consisting of 2 cycles of bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose (BEACOPPescalated) followed by two cycles of ABVD (2+2 regimen) followed by 30 Gy IFRT with 4 cycles of ABVD followed by 30 Gy IFRT. After a median follow-up of 43 months, freedom from treatment failure (FFTF) with the 2 + 2 arm was superior to the standard 4 cycles of ABVD followed by 30 Gy IFRT, mainly in patients with bulky disease. However, no difference in overall survival (OS) was observed [28]. In North America, patients with bulky mediastinal mass are typically treated with 6 cycles of ABVD followed by 30 Gy of IFRT.

Although radiation fields and doses have been reduced in recent years, there is a continued interest in further reducing treatment-related toxicity by developing radiation-free regimens. After initial studies demonstrating the feasibility of this approach, two recent randomized trials using interim PET response-adapted strategies reported results with radiation-free regimens. The United Kingdom National Cancer Research Institute RAPID study compared treatment outcome of IFRT or observation in patients with early-stage HL and negative PET scan after 3 cycles of ABVD (Fig 2A) [29]. The 3-year progression-free survival (PFS) and OS were somewhat similar, especially after excluding patients who did not receive the planned radiation therapy. Both treatment arms had PFS exceeding 90% (90.8% and 94.5% in the radiation-free and combined modality treatment respectively). The authors concluded that using PET it is possible to identify a population of patients with stage IA or IIA disease who have an excellent outcome following 3 cycles of ABVD and do not need radiotherapy. On the other hand, the EORTC H10 study used response adapted therapy to investigate whether involved node radiotherapy could be omitted, without compromising treatment outcome, in patients achieving PET negative status after 2 cycles of ABVD (Fig 2B) [30].
Patients were stratified according to baseline prognostic factors (favorable or unfavorable early stage). The 1 year PFS in patients with early favorable or early unfavorable disease who were treated with chemotherapy alone (4 or 6 cycles of ABVD) was 95%, which was slightly inferior to the PFS achieved with combined modality therapy. However, based on the number of failures (25 vs 8 in the radiation-free and combined modality treatment respectively) the authors decided to stop enrollment in the early PET-negative part of the study and to maintain combined-modality treatment as standard for early PET-negative scans.

The conclusions from the two groups that have conducted the above reported trials are different and combined modality treatment is still considered the standard of care for patients with early stage HL. However, taken together, these early results indicate that response adapted therapy can be a reasonable option for many patients with early stage HL, as long as they are informed of the small risk of lower disease control when radiation therapy is omitted. Current studies are examining the role of incorporating brentuximab vedotin in the treatment of early stage HL, aiming at further reducing the doses and cycles of chemotherapy and/or eliminating radiation therapy [31, 32]. However, this approach remains experimental.

**Advanced stage HL**

Patients with advanced stage HL are treated with a variety of combination chemotherapy regimens. The most widely used regimens worldwide are ABVD and BEACOPPescalated. BEACOPPescalated has been demonstrated a superior regimen in comparison to ABVD in terms of tumor control in randomized trials. Additionally, a recent meta-analysis showed a significantly better overall survival with BEACOPP in comparison to ABVD. [33-36]. However, because second line therapy can be curative in patients that fail ABVD and due to a higher rate of acute toxicity with the BEACOPPescalated regimen, ABVD remains an acceptable first line regimen for patients with advanced disease. In general, regardless of
the choice of the initial regimen, approximately 75% to 80% of the patients with advanced stage HL are expected to be cured.

Current strategies are evaluating the incorporation of the novel antibody-drug-conjugate targeting CD30 (brentuximab vedotin) in front line regimens. Initially, brentuximab vedotin was combined with standard ABVD, however this combination resulted in excessive bleomycin-like interstitial lung toxicity. Pulmonary toxicity was prevented by omitting bleomycin, as brentuximab vedotin was successfully combined with AVD (B-AVD) resulting in 96% complete remission rate [37]. Updated results with long-term outcome of this study were presented at the 56th ASH annual meeting. Among 26 patients treated with B-AVD, 25 were still in complete remission and only one patient had relapsed after 7 months. With a median follow-up of 31 months the 3y-failure-free survival and 3y-OS were 96% and 100% respectively [38]. A phase III trial is currently comparing the combination of B-AVD to ABVD in patients with advanced untreated HL. The German Hodgkin Study Group is investigating the novel combination of brentuximab vedotin with a modified, bleomycin-free, BEACOPP regimen.

**Relapsed and refractory HL**

Patients with relapsed or refractory HL after first line treatment are usually treated with platinum-based or gemcitabine-based salvage chemotherapy regimens, such as ifosfamide/carboplatin/etoposide (ICE), dexamethasone/high-dose Ara-C/cisplatin (DHAP), or ifosfamide/gemcitabine/vinorelbine (IGEV) followed by high dose chemotherapy and autologous stem cell transplant (ASCT). At best, this strategy can cure approximately 50% to 60% of transplanted patients [39, 40]. Two strategies are currently being investigated to improve treatment outcome of patients who do not respond to or relapse after initial therapy. The first strategy is to improve the efficacy of second line regimens by incorporating brentuximab vedotin. Results from two independent phase II studies evaluated a sequential therapy with brentuximab vedotin followed by ICE chemotherapy demonstrated 30% CR rate
with brentuximab alone, allowing patients to directly proceed with stem cell collection and ASCT without the need for ICE chemotherapy [41, 42]. While this chemotherapy-free approach is very appealing, the majority of patients required chemotherapy immediately before ASCT. Overall, 80% of patients were successfully transplanted. In a different approach, brentuximab vedotin was concurrently administered with bendamustine chemotherapy, achieving 80% CR rate [43]. At the present time, it is too early to determine which approach is superior, as long term follow up will be needed to better assess the success of these treatment strategies. Ultimately, a randomized study will be needed to better assess the contribution of these novel salvage regimens. Furthermore, as the activity and safety of the new salvage regimens improve, the role of ASCT consolidation will need to be re-examined.

In the second strategy, treatment is administered after ASCT to prevent disease progression. A recent randomized study examined this approach. In this study, 329 patients with high risk for disease progression after ASCT were randomized to receive brentuximab vedotin or placebo, for up to 16 cycles. After a median follow-up of 2 years, the median progression free survival (PFS) for patients receiving brentuximab vedotin was 65% compared to 45% for patients at the placebo arm (HR = 0.50; 95% CI, 0.36-0.70) [44]. The overall survival was 88% in both arms of the study, mainly due to the fact that the majority of patients who were initially randomized to the placebo arm received subsequent therapy, including brentuximab vedotin. As brentuximab vedotin is increasingly being combined with front-line and pre-transplant salvage regimens, the benefit of post ASCT adjuvant therapy with brentuximab vedotin may need to be re-examined in the future.

**Relapsed HL post autologous stem cell transplant**

Patients whose disease relapses after ASCT, continue to have unmet medical needs, as their median survival is shorter than 3 years. After multiple failures, new highly effective agents have been identified for the treatment of patients with relapsed HL. At present time,
the antibody-drug-conjugate brentuximab vedotin is the only drug approved by regulatory agencies for this indication. More recently, the anti-programmed death 1 (PD1) antibody nivolumab was granted an accelerated approval designation by the United States Food and Drug Administration (FDA), setting the stage for a potential future approval. Other compounds, such histone deacetylase (HDAC) inhibitors and phosphoinositide-3 kinase (PI3K) signalling pathway inhibitors have also demonstrated promising activity (Figure 3).

**Brentuximab Vedotin**

Despite our poor understanding of CD30 biologic functions, CD30 became an attractive target for the treatment with monoclonal antibodies, because of the restricted nature of its expression. After multiple failures to develop therapeutic naked anti-CD30 antibodies, subsequent strategies focused on conjugating CD30 antibodies to deliver either radio-isotopes or toxic chemicals to tumor cells. These efforts resulted in the successful development of the novel antibody-drug-conjugate brentuximab vedotin, which used the chimeric monoclonal anti-CD30 antibody, cAC10, as a backbone to carry monomethyl auristatin E (MMAE) toxic payload [45, 46]. MMAE is a synthetic tubulin inhibitor that is covalently linked to cAC10 via a maleimidecaproyl-valyl-citrullinyl-p-aminobenzylcarbamate linker [47]. The first-in-man phase-I study of brentuximab vedotin enrolled 45 patients (42 HL and 3 ALCL). Using an intravenous escalating doses every 3 weeks, the recommended phase-II dose was identified as 1.8 mg/kg every 3 weeks. Tumor regression was observed in 86% of the patients (11 complete responses and 6 partial remissions) [48]. In a subsequent, pivotal, phase 2 study, 102 patients with relapsed and refractory HL after receiving autologous stem cell transplantation (ASCT) were treated with brentuximab vedotin [49]. The overall response rate was 75% (33% CRs), and 94% of patients had tumor regression. Responses were rapid, with a median time to treatment response of 5.7 weeks and the median time to achieving complete remission of 12 weeks. With a median follow-up time of 32.7 months, the median overall survival was 40.5 months. In 2011, brentuximab vedotin was approved by the US Food and Drug Administration, and later in the EU, for the
treatment of patients with relapsed HL after ASCT and for patients with HL refractory to two lines of chemotherapy [50]. Brentuximab vedotin is generally well-tolerated with most (≥ 10%) treatment-related adverse events being peripheral sensory neuropathy (42%), and gastrointestinal symptoms. Neutropenia and thrombocytopenia were observed in 19% and 8% of patients respectively. Because most responses achieved with single agent brentuximab vedotin are partial and relatively of short duration, many investigators are currently examining new combinations of brentuximab vedotin and other active agents, such as mTOR inhibitors and HDAC inhibitors.

**Immune checkpoint inhibitors**

Regulation and activation of T lymphocytes depend on signaling by the T cell receptor (TCR) and also by co-signaling receptors that deliver negative or positive signals. Although HRS cells are surrounded by an overwhelming numbers of T cells, these T cells are immunologically tolerant, as they fail to eliminate the cancer cells. Programmed death 1 (PD1) pathway serves as a checkpoint to limit T-cell-mediated immune responses and to prevent autoimmunity (Figure 4). Many tumor cells, including HRS cells, have been shown to aberrantly express PD-L1 and PD-L2, which can inhibit T cell activation [51, 52]. Accordingly, antibodies that can block PD1/PD-L1/2 engagement may facilitate and enhance T cell activation and induction of T-cell mediated anti-tumor response. Several antibodies have been developed to either target PD1 or PDL1 for the treatment of a variety of cancer types, with two of them (nivolumab, pembrolizumab), targeting PD1, recently showing remarkable single agent activity in patients with relapsed HL (Table-2).

Nivolumab, a fully human monoclonal IgG4 antibody directed against PD-1 was tested in 26 heavily pre-treated patients with HL. Eighty-seven percent of patients treated had received three or more previous treatment regimens, 78% had failed prior BV and 78% ASCT. The response rate was 87% (95% CI, 66 to 97), with complete response observed in 4 patients (17%), partial response in 16 (70%), and stable disease in 3 patients (13%). Among 15
patients who had disease recurrence after ASCT and brentuximab vedotin, the response rate was 87% (95% CI, 60 to 98). For the 3 patients who did not undergo autologous stem-cell transplantation before brentuximab treatment, the response rate was 100% (95% CI, 29 to 100), with all 3 patients having a partial response. Among the 5 patients who did not receive brentuximab, the response rate was 80% (95% CI, 28 to 99), with 3 patients (60%) having a complete response, 1 (20%) a partial response, and 1 (20%) stable disease. The rate of progression-free survival at 24 weeks was 86% (95% CI, 62 to 95). At a median follow-up of 40 weeks (range, 0 to 75), the median overall survival had not been reached. Drug-related adverse events were reported in 18 patients (78%). The most common were rash (in 22%) and thrombocytopenia (in 17%). Drug-related grade 3 adverse events were reported in 5 patients (22%), and included myelodysplastic syndrome, pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, increased lipase level, decreased lymphocyte level, and leukopenia. There were no drug-related grade 4 or 5 adverse events [53].

Another anti-PD-1 monoclonal antibody Pembrolizumab is in clinical development in hematologic malignancies. Preliminary results on 31 patients enrolled (29 with post-baseline efficacy assessment or who discontinued therapy before week 12) were presented at the 2014 ASH annual meeting and showed a good safety profile and significant clinical activity. The overall response rate was 66% with 21% CR rate (6 patients) and 45% PR rate (13 patients). Stable disease was achieved in 21% (6 patients) while 14% had progressed (4 patients). All patients were previously treated with brentuximab vedotin and 69% had failed autologous transplant. Treatment was well tolerated and only 3 patients presented a ≥gr3 adverse event (axillary pain, hypoxia, joint swelling and pneumonitis). The most common grade 1-2 adverse events were respiratory events and thyroid disorders [54]. The results above reported are very encouraging and it is possible that anti-PD1 monoclonal antibodies will enter further clinical development in HL.
HDAC Inhibitors

Several HDAC inhibitors have been tested in patients with relapsed HL, with consistent results. Overall, most HDAC inhibitors produce favorable clinical activity, with documented tumor reduction in approximately 60-70% of patients, with an overall (partial and complete) response rates averaging 25% (Fig 3) [55]. Although the overall response rate achieved with HDAC inhibitors is lower than those reported with brentuximab vedotin and PD1 antibodies, they produce a comparable PFS. This mainly due to the fact that the depth of tumor reduction rarely correlate with PFS. On the other hand, in addition to a direct anti-tumor effect, HDAC inhibitors have favorable immune modulatory effects. HDAC inhibitors can alter the levels of cytokines and chemokines in vitro and in vivo, favoring a TH1-type immune response [56]. Furthermore, HDAC inhibitors may enhance antitumor immunity through HDAC11-mediated upregulation of OX40L on HRS cells and by downregulating PD1 on T cells [57]. Therefore, although no HDAC inhibitor has been approved by the FDA for the treatment of HL, these agents are well suited for combination strategies with chemotherapy, small molecule inhibitors, or immune therapeutic agents.

In a recent study, Oki et al combined panobinostat with standard ICE salvage chemotherapy prior to ASCT. The response rate in 21 patients treated on this phase 1 study was 81%, with 71% achieving complete remission [58]. In the post-transplant setting, the same group evaluated the novel combination of panobinostat with the mTOR inhibitor everolimus in patients with relapsed HL. The response rate in 14 patients treated was 43%, although the duration of response was relatively short [59]. In a similar study, Janku et al combined vorinostat with the mTOR inhibitor sirolimus in 57 heavily pretreated patients with relapsed HL reporting a response rate of 57% [60]. Ongoing studies, include the novel combination of mocetinostat with brentuximab vedotin. Other mechanism-based combination regimens with HDAC inhibitors should also be examined in future clinical trials.
Conclusion

The approval of brentuximab vedotin for the treatment of patients with relapsed HL after ASCT and for patients refractory to two lines of chemotherapy has opened new roads for the development of new brentuximab vedotin-based treatment strategies in HL (Fig 5A). Current trials are evaluating different treatment modalities incorporating brentuximab vedotin with a variety of agents. Results of these studies may change the current standards of care for patients with HL. With the encouraging results observed with PD1-targeted agents, new treatment paradigms will soon emerge (Fig 5B). Ultimately, the standard of care will continue to change as we pursue more effective and less toxic treatment regimens.
Tables and Figures titles and leggends:

Table-1. Prognostic factors in early stage HL

Table-2. Activity of PD1-targeted therapy in relapsed HL

Figure-1: Treatment options for patients with early stage HL
XRT: Radiation therapy

Figure-2A: RAPID trial design

Figure-2B: H10 trial design

Figure 3: Response rates of novel agents in patients with relapsed HL.
Results are compared to those achieved with the combination chemotherapy regimen GVD (Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin).

Figure-4. Interactions between T lymphocytes and HRS cells through the PD1 pathway.

Figure-5A: New brentuximab vedotin-based treatment strategies.

Figure-5B: New treatment paradigms.
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Early stage HL

- Favorable: ABVD x 2 + 20 Gy XRT
- Unfavorable: ABVD x 4 + 30 Gy XRT
- Bulky mediastinal: ABVD x 6 + 30 Gy XRT
- Radiation-free approach: ABVD x 6
- Interim PET guided approach: esBEACOPP x 2 + ABVD x 2 + 30 Gy XRT
Stage I A or IIA (favorable or unfavorable prognosis based on EORTC criteria)

3x ABVD

PET

PET negative (Deauville score 1-2)
Randomization
Observation

PET positive (Deauville score 3-5)
1x ABVD + IFRT

IFRT
Brentuximab Vedotin + PD1/PDL1 antibody

HDACi

PI3K/mTORi

Chemotherapy
### EORTC

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<td>4. Age ≥ 50 years</td>
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EORTC: European Organization for Research and Treatment of Cancer  
GHSG: German Hodgkin Study Group  
ESR: Erythrocyte sedimentation rate
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ORR: Overall response rate  
CR: Complete response  
BV: Brentuximab vedotin  
iv: Intravenously