Other New Agents for Hodgkin Lymphoma

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24.1 PI3K/Akt/mTOR Pathway

Constitutive activation of the PI3K/Akt/mTOR pathway is present in both HL cell lines and primary tissue [1, 2]. The significance of this pathway in HL was demonstrated by the efficacy of everolimus, an mTOR inhibitor, in patients with relapsed or refractory (rel/ref) HL. In the phase II study evaluating everolimus in rel/ref HL, patients received 10 mg/day until progression of disease [3]. Among the 57 patients enrolled, the overall response rate (ORR) and complete response (CR) rate were 45.6% and 8.8%, respectively. Seven (12%) patients were long-term responders (lasting >12 months). Treatment was well tolerated with grade 3 or 4 thrombocytopenia and anemia occurring in 21% and 14%, respectively. Furthermore, only 3.5% of patients experienced grade 3 stomatitis, and pneumonitis occurred in 10.5% (all grade 1 or 2).

The value of targeting this pathway in HL was further tested through a phase II study evaluating idelalisib, a delta-specific PI3 kinase (PI3Kδ) inhibitor. PI3Kδ is preferentially expressed in cells of hematopoietic origin, particularly B cells, and is highly expressed in HL cell lines compared to other PI3K isoforms [4]. Twenty-five patients with rel/ref HL enrolled on this study and were treated with idelalisib 150 mg BID until progression, with the option to increase to 300 mg BID. The ORR was 20% with one complete response and four partial responses [5]. As was seen with everolimus, a few prolonged responses were observed and median duration of response was 8.4 months. Adverse events typically seen with this drug class were observed and included grade ≥ 3 elevations in ala-

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nine aminotransferase and/or aspartate aminotransferase in five patients, colitis (grade 1 or 2) in three patients, and grade 2 pneumonitis in one patient.

Preclinical studies have led to several clinical trials evaluating novel regimens involving drugs affecting the PI3K pathway. For example, the demonstration of synergy between everolimus and panobinostat in HL cell lines led to a phase I/II study evaluating this combination [6, 7]. This combination, however, did not appear to be more efficacious than observed with either drug alone. There is also rationale for combining PI3K pathway inhibitors and immunotherapeutic agents. PI3K blockade inhibits regulatory T cells and reduces anti-inflammatory cytokines; therefore PI3K inhibitors likely function in part through promotion of antitumor immunity and have potential to synergize with PD-1 blockade [8, 9]. Pembrolizumab plus idelalisib is being evaluated in a study for chronic lymphocytic leukemia and indolent B-cell non-Hodgkin lymphomas (NCT02332980). In addition, a study evaluating PD-1 blockade plus everolimus for solid tumors is underway (NCT02890069). If these combinations are found to be safe, it would be reasonable to evaluate them in HL as well.

24.2 HDAC Inhibitors

The histone deacetylase (HDAC) inhibitors target both HL Reed-Sternberg (RS) cells and their tumor microenvironment and therefore are particularly attractive agents for HL. Their epigenetic effects on gene expression support apoptosis of RS cells and cause disruption of the cytokine- and chemokine-mediated interactions between the RS cells and their microenvironment [10, 11]. The available HDAC inhibitors differ by their specificity for particular HDAC isotypes, and the more selective HDAC inhibitors may have the advantage of causing less hematologic toxicity.

Both pan-HDAC inhibitors (vorinostat and panobinostat) and more selective inhibitors (mocetinostat and entinostat) have been evaluated in HL. Vorinostat demonstrated only modest activity in rel/ref HL in a phase II study by the Southwest Oncology Group (SWOG), with only 1 out of 25 patients achieving PR [12]. Panobinostat demonstrated more promising activity in an international phase II study in rel/ref HL [13]. Of 129 patients, there were 35 (27%) responses, which included 5 (4%) CRs and 30 (23%) PRs. Furthermore, tumor reductions were observed in 74% of patients. Responses were durable with median duration of response of 6.9 months. Common toxicities seen with this agent were thrombocytopenia (79% grade 3/4), diarrhea, nausea, and fatigue.

Mocetinostat, which selectively inhibits class I and IV HDACs, was evaluated in 51 patients with HL and demonstrated an ORR of 33% [14]. In contrast to panobinostat, hematologic toxicity was rarely seen with mocetinostat; however, 6% of patients developed nonfatal pericardial effusions. Entinostat, a selective class I HDAC inhibitor, demonstrated an ORR of 12% (6 PRs among 49 patients) and tumor reductions in 58% of patients [15].

Overall, the HDAC inhibitors consistently demonstrate activity in HL and cause only moderate toxicity; therefore, they are good candidates for evaluation in combination with other agents for HL. Their role in enhancing antitumor immunity through activating natural killer cell-mediated cell killing provides rationale for combination with PD-1 blockade [16]. An ongoing phase II study with pembrolizumab plus entinostat in Hodgkin lymphoma and follicular lymphoma is testing this concept (NCT03179930).

24.3 Lenalidomide

The antitumor activity of lenalidomide in HL is potentially mediated through activation of the E3 ubiquitin ligase cereblon, resulting in direct cytotoxicity, alteration of tumor cell microenvironment, and/or antiangiogenesis [17, 18]. Evidence of activity of lenalidomide in HL was initially reported by Böll and colleagues among 12 patients with rel/ref HL treated on a named patient program; all of the patients achieved clinical benefit and 50% achieved objective responses [19]. One patient achieved a complete response which was ongoing after 2 years of therapy. In a larger phase II study of 36 patients with rel/ref HL, lenalidomide induced objective responses in seven (19%) patients. An additional five (14%) patients achieved stable disease for 6 months or more, and prolonged responses were observed yielding a

Table 24.1 Summary of newer agents for Hodgkin lymphoma (other than brentuximab vedotin and PD-1 inhibitors)

Class	Drug	*n*	ORR (%)
HDAC inhibitor	Vorinostat [12]	25	4
	Panobinostat [13]	129	27
	Mocetinostat [14]	51	33
	Entinostat [15]	38	12
mTOR inhibitor	Everolimus [3]	57	45.6
PI3K inhibitor	Idelalisib [5]	25	20
Immunomodulator	Lenalidomide [20]	36	19

median time to treatment failure of 15 months [20]. Although not tremendously active as a single agent in HL, lenalidomide produces durable responses and represents another good candidate for combination. Lenalidomide has been evaluated in combination with everolimus as well as panobinostat; however neither combination appears more active than the individual agents [21, 22]. Ongoing studies are evaluating lenalidomide in combination with nivolumab (NCT03015896) and brentuximab vedotin (NCT03302728).

24.4 Emerging Therapies

Newer methods for targeting CD30 are under investigation and include chimeric antigen receptor (CAR)-T cells and bispecific antibodies. An initial phase I study evaluating anti-CD30 CAR-T cells demonstrated only limited activity in HL, likely due to lack of pre-CAR-T lymphodepleting chemotherapy [23]. Lymphodepleting chemotherapy improves CAR-T cell expansion and is incorporated into two ongoing studies which show promising activity in small numbers of patients so far [24–26].

AFM13 is a bispecific antibody construct that binds CD30 on tumor cells as well as CD16A on NK cells. It works by enhancing NK cell-mediated tumor cell killing. A phase I study of AFM13 showed single-agent activity in relapsed and refractory HL and it is currently being evaluated in combination with pembrolizumab [27, 28]. The combination is well-tolerated and interim results show ORR and CR rates of 87% and 35% among 23 evaluable patients.

CD25 is another promising target for HL, given that it is expressed on both Hodgkin Reed-Sternberg cells and regulatory T cells. ADCT-301 (camidanlumab) is an antibody-drug conjugate comprised of an anti-CD25 monoclonal antibody conjugated to the pyrrolobenzodiazepine dimer (PBD) toxin. In a phase I study, 60 patients with HL were treated and ORR rate among evaluable patients ($n = 55$) was 69% with 43.6% achieving CR [29]. Furthermore, at the recommended dose for expansion (45 μg/kg), the ORR and CR rates among 26 patients were 80.8% and 50%, respectively. Notable toxicities observed with camidanlumab included Guillain Barre (3.3%), grade 3 transaminitis (10%), and grade 3 rash (13.3%). A phase II study further evaluating efficacy and toxicity of this agent in HL is planned (Table 24.1).

24.5 Conclusion

Even with the availability of BV and anti-PD1 antibodies, there is considerable room for improvement in the treatment of HL. In the rel/ref setting, treatment options eventually become exhausted as patients ultimately progress following BV or anti-PD1-based treatment. Furthermore, more individualized and better-tolerated therapies are needed in the frontline and second-line treatment setting for HL. Therapies currently under investigation in HL target activated pathways within the RS cells, the HL microenvironment, or both, and the key challenge will be to identify markers that predict likelihood of response and to determine the optimal way to combine these agents to produce well-tolerated, effective regimens. As we continue to develop new effective agents for HL, emerging biomarkers, such as circulating tumor DNA [30], will undoubtedly aid us in identifying the right patient for the best treatment at the optimal time (Figs. 24.1 and 24.2).

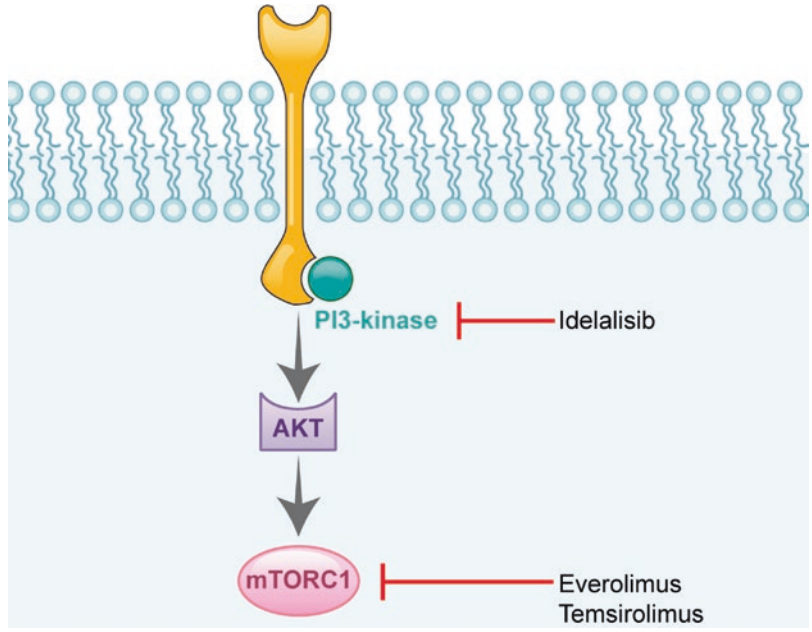

Fig. 24.1 Targeting the PI3K Pathway in Hodgkin lymphoma

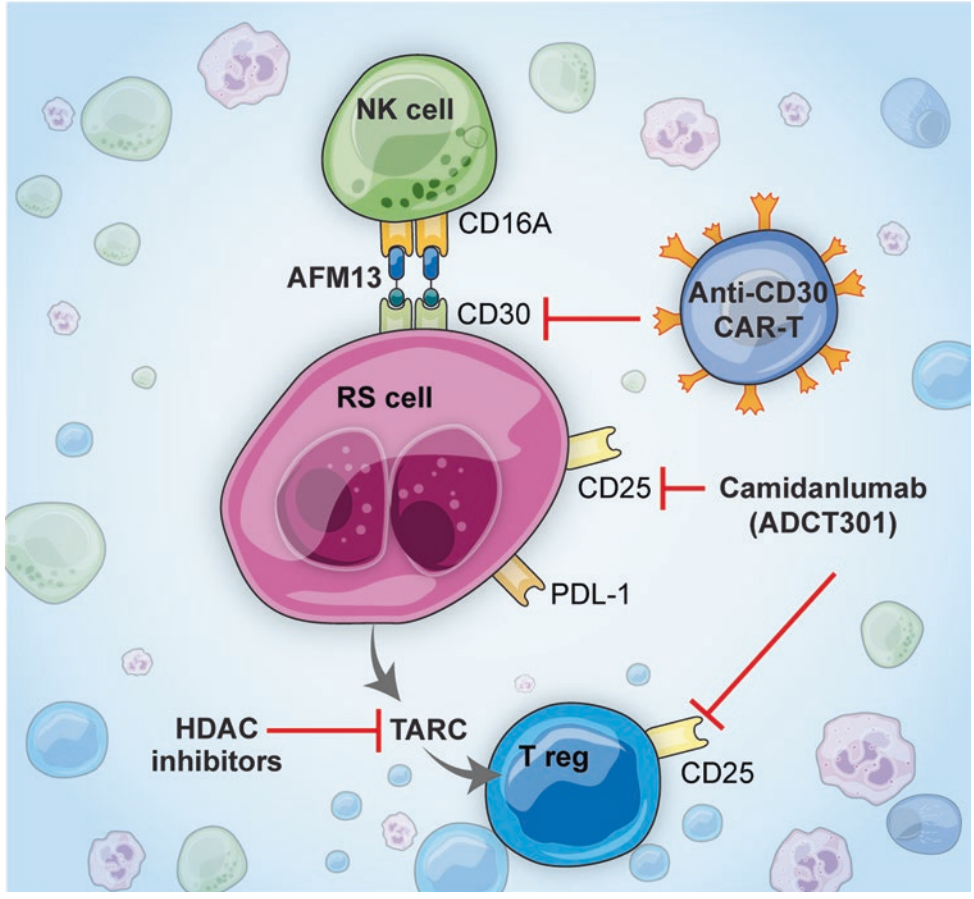

Fig. 24.2 Targeting Reed-Sternberg cells and the microenvironment

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