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Editorial

Introduction to a review series on Hodgkin lymphoma: change is here

Hodgkin lymphoma (HL) represents one of the earliest success stories of medical oncology. Following the initial demonstration that radiation therapy could eradicate early-stage disease, multiagent chemotherapy regimens were concocted and proved to be curative in a large proportion of patients with systemic spread. Doxorubicin-bleomycin-vinblastine-dacarbazine (ABVD), the most commonly used regimen for both early- and advanced-stage HL, was developed in the mid-1970s. Since that time, change has been slow to come. However, recent years have seen remarkable advances with the introduction of novel therapies and a shift in management algorithms, whereby the use of positron emission tomography (PET) is enabling response-adapted therapy.

The articles in this review series explore advances in biological insight that have led to the identification of novel targets for drug development and may enable more accurate prognostication. Optimization of therapeutic strategies for early- and advanced-stage patients, in the up-front and relapsed/refractory setting, including the role of stem cell transplantation (SCT), are examined. The reviews in this series include the following:

- Anja Mottok and Christian Steidl, "Biology of classical Hodgkin lymphoma: implications for prognosis and novel therapies"
- Paul J. Bröckelmann, Stephanie Sasse, and Andreas Engert, "Balancing risk and benefit in early-stage classical Hodgkin lymphoma"
- Sean H. Lim and Peter W. M. Johnson, "Optimizing therapy in advanced-stage Hodgkin lymphoma"
- Gunjan L. Shah and Craig H. Moskowitz, "Transplant strategies in relapsed/refractory Hodgkin lymphoma"
- Neha Mehta-Shah and Nancy L. Bartlett, "Management of relapsed/refractory classical Hodgkin lymphoma in transplant-ineligible patients"

In the first review, Mottok and Steidl highlight key aspects of HL pathobiology that may be exploited for therapeutic benefit. HL represents a unique malignancy, in which the malignant tumor cells are outnumbered by reactive immune cells in the microenvironment. Despite originating from B cells, Hodgkin-Reed-Sternberg (HRS) cells typically lack classic B-cell surface markers, but stain strongly for CD30, interferon regulatory factor 4 (IRF4), and, commonly, CD15. Approximately 40% of cases are Epstein-Barr virus (EBV)-associated. Constitutive activation of NF-κB and the JAK-STAT signaling pathway has been shown to be a hallmark of HL, but other signaling cascades can also be dysregulated, such as the phosphatidylinositol 3-kinase–AKT pathway. Expanding insight into the genetic alterations associated with these observed aberrancies and their downstream consequences has led to the discovery of numerous potential therapeutic targets. In addition to the tumor cell, the immune microenvironment plays a large role in the pathogenesis of HL and represents an additional avenue that may be therapeutically targeted. The recognition that tumor cells frequently overexpress programmed death-ligand 1 (PD-L1) and PD-L2, thereby reducing T-cell activity and escaping immune surveillance, provides rationale for the use of checkpoint inhibitors and other immune-based strategies. In light of the marked heterogeneity among patients with HL, there is a great need for reliable biomarkers that may enable better prognostication and predict response to standard or novel agents. Although ongoing efforts using genomic profiling of whole tissue, microdissected HRS cells, and peripheral blood are showing promise, clinically validated biomarkers are not yet available for routine use.

Bröckelmann, Sasse, and Engert provide a thoughtful review of management considerations for patients with early-stage HL. In these patients, outcomes are exceedingly favorable, with 5-year progression-free survival (PFS) and overall survival (OS) rates >90% and >95%, respectively. As such, the risk of long-term treatment-related morbidity and mortality presents a greater threat. The current challenge is how best to maintain treatment efficacy, while minimizing risk of toxicity. Historically, treatment of early-stage HL has relied on a combined modality approach, with chemotherapy and involved-site radiation therapy considered by many to be the standard of care. More recently, given the prognostic capacity of interim PET scanning, response-adapted strategies have been evaluated. Patients who achieve a complete metabolic response on interim PET have an OS following chemotherapy alone which is comparable to that of patients receiving combined modality. Although the omission of radiation may result in a slightly higher rate of relapse, most patients can be successfully treated with secondary therapy, thus allowing the majority of patients to be spared the toxicity of radiation. The optimal approach for early-stage HL remains controversial; however, it is likely that individualized risk- and response-adapted therapy will be used moving forward.

Lim and Johnson discuss treatment optimization for patients with advanced-stage HL, where 5-year PFS ranges from 60% to 90% following standard ABVD, depending on clinical risk according to the International Prognostic Score. Although higher-intensity regimens, such as bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), may improve PFS, the added toxicity limits the desirability of administering this to all patients. Given the prognostic utility of interim

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PET in advanced-stage HL, various PET-adapted strategies are undergoing evaluation. Recently, deescalation of therapy by omitting bleomycin has been shown to be feasible in patients who achieve a complete metabolic response following 2 cycles of ABVD. The role of escalating therapy in patients with a positive interim PET or strategies that deescalate after initial intensified therapy require further exploration. With the advent of novel therapies such as brentuximab vedotin (BV) and checkpoint inhibitors, which have demonstrated substantial efficacy in patients with relapsed/refractory HL, the next challenge will be how to best incorporate these into upfront treatment. Recently, the Echelon-1 trial demonstrated improved modified PFS with the combination of brentuximab and doxorubicin, vinblastine, and dacarbazine (AVD), compared with standard ABVD. The clinical benefit of this novel regimen will need to be weighed against its additional cost and toxicity to assess whether this should become the new standard of care.

Patients who fail initial therapy can be cured with secondary attempts. Shah and Moskowitz review strategies to improve outcomes in this setting. Non–cross-resistant salvage therapy followed by dose intensification and autologous SCT (ASCT) offers the best chance of cure. Given the young median age of patients with HL, such an approach is feasible in the majority of patients. There is no standard salvage regimen prior to ASCT, but patients who achieve a complete metabolic response pretransplant exhibit the best outcomes. Thus, improving salvage therapy with the incorporation of novel agents would seem to be a rational goal. Numerous trials evaluating the merit of novel combinations in the pretransplant setting are ongoing with initial encouraging results. However, comparative trials have not been reported and the impact on long-term outcomes remains unknown. The use of BV maintenance therapy posttransplantation was recently evaluated in a randomized phase 3 trial in patients with high-risk features, resulting in a significant improvement in PFS. Although no difference in OS was observed, this analysis was limited by short follow-up and the potential for patients in the placebo arm to receive brentuximab at relapse. Allogeneic SCT can offer an additional curative option for some patients who fail ASCT; however, in light of the availability of novel agents, the role and timing of allogeneic SCT are uncertain.

The ongoing challenge of how best to manage patients who fail SCT or who are ineligible for intensive approaches is explored by Mehta-Shah and Bartlett. Many of these patients are elderly with poor treatment tolerance, or have received multiple lines of therapy and may have poor marrow reserve. Historically, treatment in this setting has involved the palliative administration of sequential single-agent chemotherapy, with the aim of prolonging disease control and maximizing quality of life. More recently, the availability of novel therapies such as BV and checkpoint inhibitors has dramatically changed the outlook for these patients. BV was initially approved by the US Food and Drug Administration (FDA) in 2011 (and shortly thereafter by the European Medicines Agency [EMA]) for patients with relapsed/refractory HL following an ASCT or 2 prior lines of therapy based on a pivotal phase 2 trial in which an impressive overall response rate of 75% (and complete response rate of 33%) was observed. Interestingly, long-term follow-up indicated that ~25% of patients who achieved a complete remission remained free of disease, suggesting that a minority of patients may be cured. More recently, the PD-1 inhibitors nivolumab and pembrolizumab have also been approved for relapsed/refractory HL based on phase 2 data indicating high response rates (~65% overall response rate), many of which were durable. Currently, efforts are under way to evaluate these agents within novel combinations and to assess their role earlier in the management algorithm. Despite these advances, there remains an ongoing need for novel approaches in HL, and efforts exploring cellular therapies such as chimeric antigen receptor T-cell therapy or autologous EBV-directed cytotoxic T lymphocytes show promise for the future.

After years of the status quo in HL, change is finally here. Yet, moving forward, the dilemma remains the same. How can we best treat individual patients such that efficacy is maximized and toxicity is minimized? Development of reliable biomarkers to better assess risk at diagnosis and to guide selection of therapy will be imperative in order to enable personalized therapy for patients with HL. Furthermore, efforts to improve response assessment through innovative PET approaches or molecular assays such as circulating tumor DNA may enable real-time response-adapted therapy, guiding both drug selection and duration of therapy.

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