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Relapsed and Refractory Hodgkin Lymphoma

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Introduction

The management of relapsed and refractory (rel/ref) Hodgkin lymphoma (HL) has changed dramatically with the availability of brentuximab vedotin (BV) and checkpoint inhibitors. The data leading to approval of these agents and their incorporation into the treatment paradigm of rel/ref HL will be discussed.

Brentuximab Vedotin

The pivotal study that led to FDA approval of BV enrolled 102 patients with rel/ref HL following failure of ASCT.[1] Patients were treated with BV 1.8 mg/Kg intravenously every 3 weeks for up to 16 doses. The overall response rate (ORR) was 75% and complete response (CR) rate 34%. Five-year follow-up for this study demonstrated durable benefit for select patients. In particular, 5-year progression free survival (PFS) for patients achieving CR was 52% and 9% of patients remained in remission following BV despite never receiving additional therapy.[2]

Checkpoint Inhibitors

In the pivotal phase II study, nivolumab was evaluated in 80 patients with rel/ref HL who had failed both ASCT and BV. Nivolumab was administered at 3 mg/kg every 2 weeks and objective responses were seen in 66%, including 9% with CR.[3] This data led to FDA approval of nivolumab for rel/ref HL following ASCT and BV in May 2016. Based upon data from another cohort from the study, the approval was subsequently extended to include patients who had relapsed or progressed after 3 lines of therapy that includes ASCT. Similar efficacy was seen in the phase II study evaluating pembrolizumab, 200 mg every 3 weeks, in which 69% patients achieved objective response and 22% achieved complete response. Based upon these results, pembrolizumab received FDA approval for treatment of patients with rel/ref HL who relapsed or progressed after three or more previous lines of therapy in March 2017.[4]

Second-line Therapy

Up to 30% of patients with HL fail front-line therapy due to rel/ref disease.[5] Randomized studies have established the standard therapy for these patients to be salvage chemotherapy followed by ASCT.[6,7] The choice of salvage therapy for HL is center or investigator dependent and options include platinum-based regimens such as ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, cytarabine, cisplatin) or ESHAP (etoposide, cytarabine, cisplatin, methylprednisolone), and gemcitabine-based regimens such as IGEV (ifosfamide, gemcitabine, etoposide), GDP (gemcitabine, dexamethasone, cisplatin), or GVD (gemcitabine, vinorelbine, doxil).[8-12] Studies have consistently shown that pre-transplant PET normalization is one of the strongest predictors of outcome

following ASCT and thus should be the goal of salvage therapy prior to ASCT.[13-19]

Recent studies have focused on evaluating novel agents in the pre-transplant salvage setting, with the goal of improving rates of PET-normalization and treatment tolerability. BV has been studied in combination with chemotherapy, such as bendamustine, ICE, DHAP, and ESHAP.[20-22] In addition, BV has been studied as a single-agent given sequentially with combination chemotherapy for patients who remain PET-positive after BV.[23,24] Although some of these studies are still ongoing, both combination and sequential approaches with BV produce CR rates ranging from 69% to 90%. Finally, in an ongoing study for patients who relapsed or progressed following front-line therapy, BV is being evaluated in combination with nivolumab and among 59 evaluable patients so far, 63% have achieved CR.[25]

Post-ASCT Maintenance Therapy

Up to 50% of patients who undergo ASCT for rel/ref HL relapse and therefore strategies to reduce the risk of relapse following transplant have been explored.

The AETHERA study was a randomized, double-blind phase 3 trial in which 329 HL patients who had undergone ASCT and were at risk of relapse (due to presence of extranodal disease, relapse within 1 year of initial treatment, or primary refractory disease) were randomized to either 16 cycles of BV or placebo.[26] Median PFS in the BV group was 42.9 months compared to 24.1 months for the placebo group (p=0.0013). Based upon this data, the FDA extended the label for BV to include post-ASCT maintenance for up to 16 doses and this is a reasonable strategy to consider for patients at higher risk of relapse after ASCT.

Treatment of rel/ref HL after ASCT

Prior to the availability of checkpoint inhibitors, common practice for patients who relapsed after ASCT was additional therapy aimed to induce remission followed by consolidation with reduced intensity condition allogeneic stem cell transplant (RIC-SCT). Outcomes with RIC-SCT vary widely among prospective studies with 3 to 4-year PFS ranging from 26-54%[27-29].

The role of RIC-SCT is less clear with the availability of nivolumab and pembrolizumab. One reason for this is the concern that patients who have been treated with checkpoint inhibitors are more prone to high grade graft-versus-host-disease (GVHD).[30] Furthermore, many patients who respond to nivolumab or pembrolizumab have minimal treatment-related side effects, durable responses, and good quality of life, and therefore the best timing for RIC-SCT, which may be associated with significant toxicity, is unclear. Due to these issues, the decision to proceed to RIC-SCT for HL patients responding to checkpoint inhibitors is an individualized decision.

Conclusion

With the approval of BV and checkpoint inhibitors, the management of rel/ref HL has evolved significantly. The survival for patients relapsing after ASCT is improved because of the availability of these agents. Furthermore, the use of these agents in the second-line setting is associated with high PET-negative rates and thus likely improved outcomes after ASCT. Ongoing and future studies will continue to evaluate strategies of incorporating these agents in the rel/ref as well as front-line settings and ultimately improve efficacy and tolerability of treatment for HL.

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