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The Bottom Line

Check-Point Inhibitors before and after Allogeneic Hematopoietic Stem Cell Transplant: The Double-Edge Sword



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Co-inhibitory signaling pathways play a pivotal role in hampering immune responses in cancer patients, enabling tumor escape. In hematologic malignancies, allogeneic hematopoietic stem cell transplantation (allo-HSCT) was the first immunotherapy to demonstrate clinical efficacy with a potential to cure. More recently, clinical trials with antibodies targeting both the PD-1 and CTLA-4 pathways demonstrated efficacy, with durable remissions in a proportion of patients, in a variety of solid tumors, and more recently in hematologic malignancies [1]. The early encouraging signal seen with check-point inhibitors (CPIs) in hematologic malignancies has led to the opening of several clinical trials with CPIs in many hematologic malignancies [2]. This rapidly evolving treatment paradigm with the use of CPIs in patients with hematologic malignancies creates a 2-fold challenge for transplant physicians: (1) many patients enrolled in studies with CPIs will become allo-HSCT candidates at some time during their disease course, and (2) despite the curative potential of allo-HSCT, relapse remains the primary reason for failure and CPIs (specifically CTLA4 inhibition) may have a specific benefit in post allo-HSCT relapse [3], resulting in more patients with post allo-HSCT relapse being enrolled in CPI clinical trials.

In the article accompanying this editorial, Ijaz et al. [4] summarize the results of a comprehensive literature review of 24 selected articles (13 case reports and 11 original manuscripts), analyzing the use of CPIs in hematologic malignancies before and after allo-HSCT. The study included 107 patients who received a CPI before allo-HSCT and 176 patients after allo-HSCT. The patients received different PD-1 or CTLA-4 monoclonal antibodies at various doses; however, the most commonly used CPI was nivolumab in 91 of 107 pre-HSCT and

62 of 150 post-HSCT patients. The most common indication for CPI use was Hodgkin lymphoma. The authors reported an overall response rate (ORR) of 68% (47% CR) in pre-HSCT patients and 48% to 88% (28% to 58% CR) in post-HSCT patients treated with CPIs. In the 107 patients who received CPIs before allo-HSCT, 56% developed acute graft-versus-host disease (GVHD) with 12 GVHD-related deaths. In the 176 patients who received CPIs after allo-HSCT, for relapse, 13% to 19% developed acute GVHD with 11 GVHD-related deaths.

This study suggests considerable risks of acute GVHD associated with the use of CPIs before and after HSCT despite their potential efficacy. A high incidence of GVHD with the use of CPIs in the peri-transplant setting has been reported in the studies [3,5–7]. However, there have been observations that the risk of GVHD may vary based on the allograft donor source, the type of post-HSCT GVHD prophylaxis, prior history of GVHD, immunosuppression at time of CPI administration, and dosing schedules and number and duration of CPI use. In the pre-HSCT setting, Merryman et al. [5] reported lower rates of grade 3–4 acute GVHD in 11 patients receiving bone marrow (BM) grafts compared with peripheral blood stem cells (PBSCs) (0% versus 32%) in a series of 39 patients. This difference was donor independent. More recently, Schoch et al. [8] showed that there was no grade 3–4 acute GVHD observed in a series of 14 patients treated with CPIs prior to allo-HSCT who received post-transplant Cytosine Arabinoside (PTCy) as GVHD prophylaxis. Most patients, 12 of 14, had BM as the hematopoietic stem cell source. We had a similar observation in 43 AML/MDS patients who received PD-1- or CTLA-4-based therapies prior to allo-HSCT. Grade 3–4 acute GVHD (aGVHD) by day 100 was only 5% with the use of PTCy as GVHD prophylaxis compared with 22% with non-PTCy GVHD prophylaxis. Interestingly, progression-free survival at 1-year was also improved with the use of PTCy as 56% versus 25% [9].

In the post-transplant setting, the history of GVHD may predict the risk of developing/flaring GVHD after CPI introduction following allo-HSCT. Herbaux et al. [7] reported aGVHD in 30% of Hodgkin lymphoma patients, occurring within 1 week after the first infusion of nivolumab. All 6 patients with aGVHD after nivolumab had a prior history of aGVHD. They did not observe GVHD among patients without history of GVHD.

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Similarly, Haverkos et al. [6] showed that the majority of CPI-emergent GVHD occurred in patients with a prior history of GVHD, with a few new cases of GVHD in patients without a prior history of GVHD observed. Herbaux et al. [7] also reported that none of the 4 haploidentical related transplants who received PTCy GVHD prophylaxis developed GVHD after CPI use, suggesting a potential protective role of PTCy GVHD prophylaxis even in the setting of CPI use after allo-HSCT.

More data is needed to determine whether the risk of GVHD can be modified by patient and/or transplant-related characteristics; however, there has been a concern that improving GVHD incidence could compromise the allo-HSCT efficacy in patients who received pre-HSCT CPIs. The authors in this article have observed an increased rate of efficacy with a graft-versus-tumor effect associated with an increased risk of GVHD. Previous studies [3,5] have shown that the post-HSCT circulating T cell subsets have an altered immunologic profile in patients previously treated with a CPI. Patients were observed to have a decreased Treg:CD4Tcon ratio that was associated with an increased incidence and severity of GVHD. However, the authors also noted that the decreased Treg:CD4Tcon ratio was associated with clinical response suggesting an augmented graft-versus-tumor effect.

There are currently many questions regarding the safest and most efficacious approach to incorporating CPIs in the treatment of patients with hematologic malignancies who are either candidates for allo-HSCT or just relapse following allo-HSCT. The sample sizes and follow-ups in the reported studies limit our ability to reach any clear conclusion. With numerous ongoing studies across hematologic malignancies (lymphoma, AML, MDS) that incorporate CPIs in the frontline or the salvage setting before allo-HSCT and limited options for therapy for post allo-HSCT relapse, we need a collaborative effort to collect the transplant data prospectively including immunologic correlates, not only in the peripheral blood but also in the tissue compartments. This may help us more clearly understand which patient populations are more likely to benefit from CPIs,

and determine the optimal timing and number of doses of CPI treatment and GVHD prophylaxis to subside the risk of GVHD.

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