

## REVIEW ARTICLE

# Post-hematopoietic stem cell transplantation relapse: Role of checkpoint inhibitors

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## Abstract

**Background and Aims:** Despite the revolutionary effects of hematopoietic stem cell transplantation (HSCT) in treating hematological malignancies, post-HSCT relapse is considered a critical concern of clinicians. Residual malignant cells employ many mechanisms to evade immune surveillance and survive to cause relapse after transplantation. One of the immune-frustrating mechanisms through which malignant cells can compromise the antitumor effects is misusing the self-limiting system of immune response by overexpressing inhibitory molecules to interact with the immune cells, leading them to so-called “exhausted” and ineffective. Introduction of these molecules, known as immune checkpoints, and blocking them was a prodigious step to decrease the relapses.

**Methods:** Using keywords *nivolumab*, *pembrolizumab*, and *ipilimumab*, we investigated the literature to figure out the role of the immune checkpoints in the HSCT setting. Studies in which these agents were administered for relapse after transplantation were reviewed. Factors such as the interval from the transplant to relapse, previous treatment history, adverse events, and the patients' outcome were extracted.

**Results:** Here we provided a mini-review discussing the experiences of three immune checkpoints, including nivolumab, pembrolizumab, and ipilimumab, as well as the pros and cons of using their blockers in relapse control after HSCT. In conclusion, it seems that CI therapy seems effective for this population. Future investigations may provide detailed outlook of this curative options.

## KEYWORDS

checkpoint blocker, hematopoietic stem cell transplantation, immune checkpoint, relapse

## 1 | INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has been proposed as a therapeutic strategy for hematological malignancies, although subsequent complications still attenuate favorable outcomes.<sup>1</sup> With the advent of non-myeloablative reduced-intensity conditioning (RIC

and allogeneic HSCT (allo-HSCT), the spectrum of patients' candidates for transplantation has been widened. However, infection, graft-versus-host disease (GVHD), and relapse are the main obstacles that decrease the success of allo-HSCT. With a 1-year survival below 20%, relapse is the most common cause of treatment failure after HSCT.<sup>2</sup> Post-transplantation strategies for reducing relapses, such as

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donor lymphocyte infusion (DLI) and donor-derived T/natural killer (NK) cell infusion, could not succeed as much as expected due to the potential complications and risks.<sup>3</sup> DLI is often limited to chronic myeloid leukemia (CML) patients due to the increasing high risk of GVHD in others<sup>4</sup>; NK cell therapy is still hesitating concerning difficulties in its expansion and standardization protocol. Therefore, a thoughtful choice of alternative treatment for post-HSCT relapse deserves more investigations.<sup>4</sup>

Survived leukemic stem cells (LSCs) from conditioning regimens and poor immune reconstitution are responsible for relapse after HSCT.<sup>5</sup> There is evidence that niche interactions between bone marrow stroma and LSCs provide protective properties against chemotherapy.<sup>6</sup> Also, one of the reasons for the resistance of LSCs is their dormant status.<sup>7</sup> Releasing exosomes and microvesicles, LSCs alter the healthy niche to leukemic-supportive microenvironment.<sup>8</sup> Thanks to the favorable effect of graft-versus-leukemia (GVL), the relapse rate is lower in allo-HSCT than autologous HSCT (auto-HSCT). Therefore, relapse may be a hint of the failure of GVL. In other words, mechanisms that increase the GVL effect can also increase GVHD, which explains why less relapse occurs in patients with a history of mild GVHD.

Immune cells have a substantial role in relapse control. Reduced dendritic cells (DCs) have been associated with relapse after HSCT.<sup>9</sup> Although regulatory T cells (T regs) effectively prevent GVHD, they may prohibit GVL.<sup>10</sup> Consistent with this, it has been demonstrated in a study that a higher dose of CD34+ cells correlates with a higher rate of relapse, which proposed that it could be due to more malignant cells and T regs, decreasing antileukemic effects.<sup>11</sup> Because of a higher percentage of T cells in peripheral blood HSCT, the relapse rate is lower at the expense of a higher incidence of GVHD.<sup>12</sup> NK cells can also be considered as another critical relapse-inhibiting agent because relapse in high-risk acute myeloid leukemia (AML) patients transplanted by killer immunoglobulin-like receptor (KIR)-ligand mismatch was 0%.<sup>13</sup> Similarly, a study conducted by Willem et al.<sup>14</sup> demonstrated that KIR/human leukocyte antigen (HLA) incompatibility has favorable effects in reducing relapse.

Sometimes, despite the sufficient number, lymphocytes are not functional due to the inhibitory interaction between leukemic and immune cells. Impaired function of B and T lymphocytes is associated with relapse after HSCT. In patients who relapsed after HSCT, bone marrow-infiltrating CD8+ T cells have a unique immunophenotype signature called "exhausted," which expresses a high level of programmed cell death protein 1 (PD1), cytotoxic T-lymphocyte-associated protein 4 (CTLA4), and/or other immune-checkpoints (CI). The presence of exhausted CD8+ T cells and the immunosuppressive state of the niche in relapsed myeloma reveal the potential of immunotherapy in preventing disease recurrence.<sup>15</sup> Regarding the checkpoint's role in various malignancies, checkpoint inhibitors (CIs) have been introduced for disease treatment and management. Evaluation of CIs in some malignancies displayed satisfactory results, especially in melanoma and lung cancers. In hematological disorders, there are growing studies aiming at the effect of CIs in relapse management. Here we reviewed the role of CIs in the HSCT setting.

## 2 | PD1 BLOCKADE IN POST-HSCT RELAPSE

Recently, the application of PD1 inhibitors in hematological malignancies has been strikingly growing. Since the Hodgkin lymphoma (HL) microenvironment demonstrates unique features, it is potentiated to get the advantage of CIs. There are a few Red-Sternberg cells and numerous ineffective immune cells in the lymphoma niche.<sup>16</sup> Therefore, most of the investigations are focused on refractory/relapsed HD (R/R HD).

It has been reported that the expression of inhibitory molecules, such as PD1 on the T-cell surface is associated with relapse after HSCT, independent of GVHD. The predictive value of PD1-high immune cells for leukemia relapse post-HSCT has also been suggested.<sup>15</sup> Experimental evidence supporting the role of the PD1/PD1 ligand (PDL1) pathway in post HSCT relapse is conducted by Norde et al. study, in which they observed high expression of PDL1 in CD34+ leukemic cells in relapsed patients. They reported that leukemic cells that do not express costimulatory molecules such as CD80 and CD86 make the immune system unqualified for fighting them.<sup>17</sup> Accordingly, targeting the PD1 molecular pathway by immune CIs can break tumor immune tolerance and preclude the cytotoxic T cells' deactivation.<sup>15,18</sup> Response induction of anti-PD1 therapy seems to be applied through several different mechanisms, among which the changes in transcription and translation of immune checkpoints associated genes have been demonstrated in tumor infiltrated lymphocytes.<sup>19,20</sup> Another evidence for the significance of PD1 inhibition timing, deduced from Koestner et al. experience,<sup>21</sup> in which attenuated GVL is associated with increased expression of PD1 in the allogeneic recipients. They reported that delayed adoptive transfer needs PD1/PDL1 inhibition to promote GVL effects. GVL reviving could occur by PDL1 inhibition without causing GVHD. In contrast, coadministration of PDL1 blockers with the early adoptive transfer may induce fatal GVHD, which is the main concern in using these drugs.<sup>22</sup>

Given the fact that the antitumor effects of GVL have pertained to the donor T cells, it has been concluded that PD-1 blockade could induce remission in a patient unresponsive to previous DLI therapy.<sup>23</sup> On the other hand, a recent study suggested that although CI therapy plus DLI reduce post-HSCT relapse, it also induces GVHD potential in many patients, highlighting the importance of patient selection and appropriate timing of the CI administration.<sup>24</sup> Thus, CI therapy alone may have more acceptable results than combining with DLI in some cases. Two prominent PD1 inhibitors, including nivolumab and pembrolizumab, have been investigated in transplantation studies. Here, we reviewed the literature on these CIs.

## 3 | NIVOLUMAB AND STEM CELL TRANSPLANTATION

Nivolumab, a humanized IgG4 kappa monoclonal antibody, has been approved for relapse treatment after auto-SCT since 2016.<sup>25</sup> There are many promising results about using nivolumab in post-HSCT

relapse. One prominent example was a patient with Hodgkin disease who experienced chemotherapy and relapsed after auto-HSCT. Using a PD1 blocker, 32 months after allo-HSCT, he achieved complete remission (CR).<sup>26</sup> Nivolumab induces remission in patients after auto-HSCT and failure of brentuximab vedotin, an anti-CD30 antibody.<sup>27</sup> Nivolumab demonstrated its efficiency for HD patients who experienced relapse after allo-SCT with a more acceptable risk-benefit ratio than other treatment options such as brentuximab vedotin and DLI. In this study, no GVHD was observed in patients without a history of acute GVHD.<sup>28</sup>

While most studies focused on the effect of this drug on post-transplantation relapse, there are other studies administrating nivolumab at other time points. Manson et al. study revealed that prescribing anti-PD1 before allo-SCT may increase GVL; in this condition, SCT can be considered a consolidation treatment. Notably, all the patients in their study experienced GVHD.<sup>29</sup> Similarly, another study on the 74 R/R HL suggested allo-SCT as a suitable consolidation therapy.<sup>30</sup> Sindel et al.<sup>31</sup> demonstrated that pretransplantation administration of nivolumab resulted in a cytokine storm, which could be controlled by ascorbic acid. Also, a high risk of early immune toxicity was reported from a study conducted on 39 cases.<sup>32</sup> As an effort to find other suitable timing of PD1 inhibitors, a 2017 study explained the beneficial effect of nivolumab plus brentuximab. It could pave the way for transplantation for R/R HL patients who are SCT-ineligible.<sup>33</sup>

While most investigations have been done on R/R HD, several studies reported the experience of nivolumab therapy in different hematological disorders. A study conducted on AML patients using nivolumab as a first-line treatment indicated that it does not increase the incidence of grade 3–4 GVHD.<sup>34</sup> Wang et al. demonstrated the importance of the timing of nivolumab administration in AML patients as maintenance treatment; all cases showed immune-related adverse events. The author suggested that high toxicity would observe when nivolumab began 7.8 months after allo-SCT.<sup>35</sup>

One of the rare challenges after allogeneic transplantation is post-transplantation lymphoproliferative disorders (PTLD), which result from disrupted immunological surveillance. The main factors that affect the occurrence of PTLD are the type of donor and the T-cell depletion method. The rate of PTLD after allo-HSCT has been reported as below: 4%–10% unrelated donor transplantation and 1%–3% matched related donor.<sup>36</sup> While most previous studies have examined the impact of this drug on the recurrence of the primary disease, another group of investigators administrated PD1 inhibitors in transplantation lymphoproliferative disorders (PTLD). Nivolumab successfully induced immune response in a patient diagnosed with myelofibrosis and experienced HL-like PTLD.<sup>37</sup> Another successful treatment of PTLD with nivolumab was achieved by Wada et al.<sup>38</sup> with the cost of liver toxicity. A similar indication of nivolumab was reported from a pediatric setting. An 11-year-old child diagnosed with primary CML demonstrated primary central nervous system PTLD. This girl was responsive to nivolumab after the failure of methotrexate and rituximab<sup>39</sup> (Table 1).

## 4 | PEMBROLIZUMAB AND STEM CELL TRANSPLANTATION

### 4.1 | Introduction and approval Hodgkin lymphoma

Another PD1 inhibitor agent is pembrolizumab which is a humanized IgG4 antibody. Pembrolizumab is approved for relapsed or refractory classical Hodgkin lymphoma in 2020. Clinical trials approved administration of 200 mg every 3 weeks is effective for relapsed Hodgkin lymphoma.<sup>65</sup> The results of clinical trials led to the approval of this new agent.<sup>66</sup> An analysis conducted by Armand et al. demonstrated that receiving pembrolizumab after SCT seems beneficial with a 73% of overall response rate (ORR), 59% partial remission, and 14% complete remission. They also could show that this medication induces upregulation of IFN-gamma.<sup>67</sup> In a report of two cases of HL after allo-SCT, safe and successful treatment was obtained by achieving partial and complete remission.<sup>68</sup> Chan et al. shared their results on using CI agents before auto-SCT. Evaluation of pembrolizumab therapy in 5 R/R HL patients with a history of failure in different treatment strategies showed 100% ORR and almost no toxicity was observed.<sup>69</sup> Strengthening the immune system is always likely to cause unwanted side effects, as some degree of autoimmunity, which can sometimes be a disaster for the patient. The first fatal GVHD after pembrolizumab treatment was reported in 2016. The patient died due to skin and lung chronic GVHD.<sup>70</sup> Another evidence is a report of post-pembrolizumab insulin-dependent diabetes in a 12-year-old boy with a history of disease recurrence after auto-SCT. Getting rid of lymphoma came at the cost of developing diabetes for this patient, highlighting the importance of cautiousness when applying CI agents in the pediatric setting.<sup>71</sup> In this regard, the findings of a study that revealed two death out of three indicate the importance of dose optimizing in preventing complications.<sup>72</sup>

### 4.2 | Pembrolizumab and SCT in other leukemia/lymphoma

Like nivolumab, the number of studies on pembrolizumab in HL is much higher than in other blood disorders. Recently, various hematological diseases were added to the list of research on pembrolizumab's role in their treatment. Frigault et al. examined 29 diffuse large B-cell lymphoma patients who received pembrolizumab to evaluate the effect of this CI as consolidation treatment after auto-SCT. Since the 18-month progression-free survival was 59%, it can be concluded that the results are not very satisfactory.<sup>68</sup> Promising results have been detected in the anaplastic large-cell lymphoma patients. A study reported that a relapsed patient with the previous auto- and allo-SCT was asymptomatic after receiving pembrolizumab. Though, it should be noted that she experienced hepatic GVHD.<sup>73</sup> In the case of NK/T lymphoma, the patient who received pembrolizumab before manipulated haploidentical transplantation achieved an almost complete response.<sup>74</sup>

TABLE 1 The studies of nivolumab after relapse of HSCT

Author	Year	Patients	Diagnosis	DLI	Outcome	Comment	Ref.
Ansell	2015	18 with previous auto-SCT	HL	+	ORR of 87% and a rate of PFS of 86% at 24 weeks, Beneficial	Auto-SCT, relapse	[40]
Dada	2016	1	HL	-	Major response	Previous treatment: auto-SCT	[41]
Albring	2016	3	AML	2 cases	Three different responses: CR, disease stabilization, failed to respond	Allo-SCT, relapse	[42]
Falchi	2016	2	HL	-	High rate of complete responses	Auto-SCT, relapse,	[43]
Shad	2016	1	HL	-	No GVHD, tolerable	Auto-SCT, haploidentical allo-SCT, relapse	[44]
Klobuch	2017	2	HL	+	1 case GVHD	Allo-SCT, relapse-CI	[45]
McDuffee	2017	1	HL	+	Alive with GVHD	Allo-SCT, relapse	[46]
Bekoz	2017	57	HL	-	2 GVHD, One expired	55 previous auto-SCT, 16 previous allo-SCT	[47]
Haverkos	2017	31	29 HL/2 lymphoma	5 cases	8 cases died of GVHD (high rate of GVHD)	Allo-SCT, relapse	[48]
Jiménez-Ubieto	2017	1	HL	-	Fatal GVHD, longer interval between nivolumab and allo-SCT	Allo-SCT, relapse	[49]
Chan	2017	2	ALL	1 case	One case: hepatic cGVHD, overall beneficial	Allo-SCT, relapse	[50]
Covut	2017	5 (3 received CI before allo-SCT)	HL	-	Suitable alternative treatment	Auto-SCT, allo-SCT, relapse	[51]
Onizuka	2017	1	HL	+	Manageable GVHD	Auto-SCT, allo-SCT, relapse	[52]
Cheikh	2017	2	HL	+	One case died of GVHD	Auto-SCT, allo-SCT, relapse	[53]
Terziev	2018		Primary CNS lymphoma	-	Remission	3rd auto-SCT, relapse	[54]
Ansell	2019	87	DLBCL		Beneficial after failure of auto-SCT	Auto-SCT, relapse	[55]
Forceville	2019	2	HL	-	CMR, radiotherapy in combination with nivolumab	Auto-SCT, relapse,	[56]
Charles	2019	1	HL	-	Multi-organ failure, died	Auto and allo-SCT, CI, haplo-allo-SCT	[57]
Wong	2019	1	T-AML	-	Refractory to nivolumab	UR- allo-SCT, relapse	[58]
Lepik	2019	40	HL	-		Auto-SCT relapse	[59]
Ogasawara	2019	1	HL	-	Refractory to nivolumab, expired of relapse, GVHD	Auto & haplo-allo-SCT, relapse	[60]
Kobayashi	2019	1	HL	-	CR, myositis	Auto-SCT, Allo-SCT, relapse	[61]
Quéiro	2019	3	HL	-	In combination with radiotherapy, lung toxicity, CMR	Auto-SCT, relapse	[62]
Chan	2020	6 (11 received pembrolizumab)	HL	-	ORR: 100%, PFS: 33 months, low dose was effective	17% auto-SCT, 34% allo-SCT	[63]
Sim	2020	1	ALL	-	CR with mild cGVHD		[64]

Abbreviations: ALL, acute lymphoblastic leukemia; allo-SCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; auto-SCT, autologous stem cell transplantation; cGVHD, chronic graft versus host disease; CI, check point inhibitor; CMR, complete metabolic response; CNS, central nervous system; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; GVHD, graft versus host disease; Haplo, haploidentical; HL, Hodgkin lymphoma; ORR, overall response rate; PFS, progression-free survival; T-AML, therapy-related acute myeloid leukemia.

There are a couple of investigations on multiple myeloma patients. Bryant et al. represented a multiple myeloma patient who received pembrolizumab on +118 and developed severe neutropenia. Their results emphasize the importance of immune complications after the administration of this drug.<sup>75</sup> Another study on multiple myeloma patients indicated that pembrolizumab and lenalidomide might have a positive effect at the beginning, on the day of +14, as maintenance treatment.<sup>76</sup>

Hsiao et al. followed up two AML patients with relapse after allo-SCT that received pembrolizumab. GVHD occurred in both patients, and one of them expired. Dried eyes are documented in both of them.<sup>77</sup>

A rapid and durable response was observed after pembrolizumab administration in a Sezary syndrome patient who relapsed after allo-SCT.<sup>78</sup>

## 5 | CTLA4 BLOCKADE IN POST-HSCT RELAPSE

Cytotoxic T-lymphocyte antigen 4 (CTLA4) is an inhibitory receptor, expressed on activated memory T cells and regulatory T cells, that can bind to CD28 on immune cells and negatively regulate their excess activation and functions. Besides, CTLA4 can impair the interaction between CD28 and its costimulatory ligands (CD80 and CD86) by trans-endocytosis of CD28. The effect of donor CTLA4 polymorphisms on the transplant outcome, overall survival, and relapse have been discussed in several studies.<sup>79,80</sup> In a very recent study on the pediatric population, polymorphism in donor CTLA4 was associated with a lower rate of relapse and no increase in GVHD incidence.<sup>79</sup> CTLA4 targeting has been investigated in some HSCT conditions with controversial results. It has been shown that blocking CTLA4 in post-transplantation relapse could activate T cells,<sup>81</sup> raising the possibility of immune-related adverse effects.

Ipilimumab, a fully humanized IgG1 monoclonal antibody against CTLA4, is the first and only FDA-approved CTLA4 inhibitor for metastatic melanoma. Ipilimumab has been used for many hematological disorders after relapse. In recent years, ipilimumab has also been tried for some post-SCT relapsed hematological disorders.<sup>82</sup> Accordingly, Bashey et al. reported organ-specific immune adverse events concurrent with tumor regression in 14% of cases. However, no acute or chronic GVHD was observed.<sup>83</sup> Later, Davids et al.<sup>84</sup> proposed the late administration of ipilimumab in post-HSCT relapse for more beneficial responses. However, it should be noted that the absence of severe GVHD was one of the inclusion criteria for both of these two studies. Therefore, the previous complications of patients must be considered before patient selection for this treatment strategy. Another study has investigated ipilimumab in combination with lenalidomide for patients who relapsed after allogeneic and autologous HSCT. The response rate was higher than the expectations for allo-HSCT patients, probably due to lenalidomide addition.<sup>85</sup> Another evidence is extracted from a report by Gros et al. representing a young man with early relapse after haploidentical SCT

administered with ipilimumab on Day +63. Progressive GVHD and death occurred 19 days after receiving CI.<sup>86</sup> It can be concluded that clinicians should be cautious for ipilimumab administration after haplo-transplantation. Supporting this, another report from CI administration in a myelofibrosis patient who relapsed after second haploidentical transplantation showed autoimmune hemolytic anemia as an adverse effect of ipilimumab.<sup>87</sup>

## 6 | BTLA4 BLOCKADE IN POST-HSCT RELAPSE

B and T lymphocyte attenuator (BTLA4) is an inhibitory receptor that belongs to the super immunoglobulin family and induces its suppression effect on T cells through interaction with a receptor called herpesvirus entry mediator (HVEM).<sup>88</sup> HVEM, a member of the tumor necrosis factor receptor superfamily, is constitutively expressed on malignant cells in leukemia. Blocking this pathway is reasonable to prevent disease recurrence after HSCT. This interaction impaired the T-cell response to tumor relapse. In some patients, BTLA blocking results in more noticeable effects than PD1 therapy.<sup>88</sup>

The association between BTLA and GVHD has been discussed in preclinical investigations and showed that, in the first days after HSCT, the anti-BTLA antibody could control GVHD, maintain the GVL effect through deactivating donor T cells, and cause a relative increase in natural regulatory T cells.<sup>89</sup> Contrarily, del Rio et al.<sup>90</sup> suggested that blocking BTLA/HVEM pathway is insufficient to inhibit the infiltration and allo-reaction of donor T cells to GVHD susceptible tissues. Figuring out the exact effect of blocking the BTLA pathway on GVL and GVHD needs more investigations and an extended follow-up period.

## 7 | COMPLICATIONS OF CI THERAPY IN HSCT

A meta-analysis demonstrated rare fatal toxic effects due to CI therapy. The highest rate of complications was reported when PD1/PDL1 and CTLA4 inhibitors were administered together, which only occurred in 1.23% of patients. The most involved organs were the colon, liver, lungs, pituitary, thyroid, and skin.<sup>91</sup> Kaloyannidis et al. reported that a patient who received nivolumab before transplantation showed de novo Psoriasis Vulgaris, which resolved after auto-HSCT. It has been presumed that conditioning regimens (Melfalan) and auto-HSCT could eliminate skin complications.<sup>92</sup> A literature review by Ijaz et al.<sup>4</sup> reported 14% acute and 9% chronic GVHD, following CI therapy post-HSCT; 28% of post-allo-HSCT relapsed patients achieved complete remission.

Interestingly, it has been revealed that shorter interval between HSCT and CI administrations increases the risk of GVHD.<sup>93</sup> Other factors influencing GVHD probability include GVHD prophylaxis regimen, donor source, previous history of GVHD, and concurrent immunosuppression with CI.<sup>94,95</sup>

Further studies may shed light on the best time for starting CI therapy. There is also a lack of data regarding the appropriate dose of CI administration. Assessment of PDL1 expression on post relapse lesions by immunohistochemistry might be informative about choosing an appropriate dose of nivolumab. In the field of adoptive cell therapy, coadministration of CI agents such as anti-PD1 and adoptive T/NK cell therapy raises the cytotoxicity of effector cells and improves the efficacy of procedures.<sup>3,4</sup> These results may light the interest in adding CI therapy to other treatment approaches.

## 8 | CONCLUSION

Allogeneic transplantation is performed in patients who have already experienced one or multiple relapses before being candidates for transplantation. Therefore, they have limited therapeutic options following post-HSCT relapse because treatment options such as auto-HSCT and alternative chemotherapy have been tried for many patients. Based on previous studies, CI therapy could be a promising treatment for some relapsed patients. However, some tips should be addressed before CI prescription. (I) Administration of these medications for patients with a history of autoimmunity or severe GVHD may result in serious complications. (II) Expression assessment of the checkpoints and their ligands on malignant and immune cells seems to be necessary to achieve favorable results. (III) Type, dose, and time to start CI therapy could have a tremendous effect on the outcome. (IV) Combining two drugs for patients without favorable response after single CI therapy could be beneficial while considering the possible increase in adverse effects. Finally, leukemia/lymphoma may be weakened by HSCT, but they persist and can relapse. However, combining therapy may eliminate it entirely or make it so weak that no annoying symptoms could be observed.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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