Published in final edited form as:

Curr Opin Oncol. 2017 November ; 29(6): 474–483. doi:10.1097/CCO.0000000000000408.

Stop and Go: Hematopoietic cell transplantation in the era of CAR T cell and checkpoint inhibitors

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Abstract

Purpose of review—For several decades, hematopoietic cell transplantation has been considered the standard curative therapy for many patients with hematological malignancies. In addition to the cytotoxic effects of the chemotherapy and radiation used in the conditioning regimen, the benefits of hematopoietic cell transplantation are derived from a reset of the immune system and harnessing the ability of donor T cells to eliminate malignant cells. With the dawn of the era of immunotherapies in the form of checkpoint inhibitors and chimeric antigen receptor T cells, the role of hematopoietic cell transplantation has evolved.

Recent findings—Immunotherapy with checkpoint inhibitors is increasingly being used for relapsed Hodgkin and non-Hodgkin lymphoma after autoHCT. Checkpoint inhibitors are also being tested after alloHCT with observable benefits in treating hematological malignancies, but with a potential risk of increased GVHD and transplant-related mortality. Immunotherapy with CD19 CAR T cells are powerful options with aggressive B cell malignancies both for therapy and as induction leading to alloHCT.

Summary—While immunotherapies with checkpoint inhibition and CAR T cells are increasing being used to treat hematological malignancies, HCT remains a standard of care for most of the diseases with the best chance of cure. Combination of these therapies with HCT has the potential to more effectively treat hematological malignancies.

Keywords

Hematopoietic cell transplantation; CAR; chimeric antigen receptors; immunotherapy; checkpoint blockade

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CONFLICTS OF INTEREST STATEMENT

None

Dr. Perales has received consulting fees from Incyte, Merck, Novartis, Seattle Genetics and Servier. The other authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

AG, IP and MAP contributed to the conception and design of the work and wrote the manuscript.

INTRODUCTION

The development of immunotherapy in the form of checkpoint inhibitors and chimeric antigen receptor (CAR) T cells has provided new tools for the treatment of hematologic malignancies (1–4). These strategies have been embraced with great enthusiasm due to their potential for durable disease control without excessive long-term toxicity, and they are being actively investigated as stand-alone treatments and in combination with other agents or hematopoietic cell transplantation (HCT). In this review we will explore the evolving role of autologous and allogeneic HCT as a complementary platform for novel immunotherapies.

HEMATOPOIETIC CELL TRANSPLANTATION: GENERAL CONCEPTS AND PLATFORM FOR IMMUNOTHERAPY

Autologous HCT

Autologous HCT (autoHCT) can provide effective salvage therapy for patients with relapsed or refractory Hodgkin lymphoma (HL) and non-Hodgkin's lymphomas (NHL) (5–7), and remains a standard therapy for multiple myeloma (MM) (8, 9). Importantly, not all patients are candidates for autoHCT due to inadequate disease control or comorbidities, and post-autoHCT relapse is the most common cause of treatment failure even with the use of maintenance strategies (10, 11).

Scientific rationale supports the role of autoHCT as an ideal platform for the application of immunotherapy. The early post-autoHCT period is characterized by low disease burden as a result of conditioning chemotherapy. In turn, this tumor debulking may abrogate the immune suppression mediated by expression of PD-L1 by tumor cells, chronic antigenic stimulation, induction of T regulatory cells (Tregs) and other mechanisms (12–15). Moreover, the associated transient lymphodepletion results in elimination of Tregs that may contribute to immune suppression, high levels of homeostatic cytokines that can support NK and T cell proliferation, and gradual T cell recovery mediated by homeostatic peripheral expansion of conditioning-resistant T cells or T cells reinfused with the graft, which are mainly of effector or memory phenotype (16–21). In this unique setting, checkpoint inhibitors may serve to reinvigorate T cells that still exhibit exhaustion phenotype, whereas CAR T-cells may exhibit enhanced proliferation and efficacy due to the elimination of Tregs and cytokine sinks (17, 22).

Allogeneic HCT

While advances in the selection of recipients and donors, and improvements in the supportive care of transplant recipients have resulted in decreasing transplant-related mortality, relapse after allogeneic HCT (alloHCT) remains an important cause of mortality (23). There is a paucity of acceptable options for patients who relapse after alloHCT, and immunotherapy beyond donor lymphocyte infusion (DLI) is evolving into an option for therapy of relapse after alloHCT.

Donor T cells are central players in the immunological effects of alloHCT (24). In particular, a subset of T cells is alloreactive and can recognize HLA that are non-self as foreign (25).

These alloreactive T cells can recognize host cells, including the host-derived cancer cells, and mediate a graft-versus-tumor (GVT) effect that may eliminate residual disease after HCT and maintain lasting immunosurveillance to prevent relapse (26). However, a broader and non-tumor specific attack of the host tissue by the alloreactive T cells can also lead to potentially lethal graft-versus-host disease (GVHD) (25). Separating GVHD and GVT effects remains one of the holy grails of transplant immunologists. This is of particular relevance to the use of checkpoint inhibitors peri-alloHCT, as potential enhancement of donor derived T cells with anti-neoplastic properties that mediate GVT may be accompanied by disinhibition of alloreactive donor T cells and lead to life-threatening GVHD.

Donor Lymphocyte Infusion

Given the central role of donor T cells in the beneficial and toxic effects of alloHCT, it has been postulated that adoptive transfer of donor T cells at a point after alloHCT could provide beneficial effects like antimicrobial or GVT effects without GVHD (27–29). In one of the first reports of this approach, transfusion of donor leukocytes induced remissions in 3 patients with of chronic myelogenous leukemia (CML) that had relapsed following alloHCT (30). Two of the three patients remained alive in molecular remission for about two decades while one had a hematological relapse after 20 years and was treated again with DLI after failure with tyrosine kinase inhibitor therapies (31). This initial success of immunotherapy with DLI led to wider applications of this approach for patients who relapse after alloHCT. In an analysis of 140 patients in US centers, DLI was most successful in patients with relapsed chronic stage CML and a high percentage of patients attained complete remission (32). Remissions were also seen in a few patients with MM and myelodysplasia, but were far inferior in patients with acute leukemias. Also reported were high incidences of GVHD and pancytopenia. Response was associated with acute and chronic GVHD. In spite of a lack of uniform efficacy and high toxicity, in the absence of alternatives, DLI remains the standard of care for select patients (33). As with alloHCT, wider application of DLI is hampered by inability to separate GVHD and GVT effects. However, recent advances in the field of T cell engineering suggest that such a separation may be feasible in the context of engineered autologous or allogeneic CAR T cells products, which are characterized by narrow antigen specificity and are devoid of generalized alloreactivity.

CHECKPOINT INHIBITION AND AUTOHCT (Table 1)

Hodgkin lymphoma

Hodgkin cells express high levels of PD-1 ligands as a result of chromosome 9p24.1 amplification or other aberrations, and enhanced JAK-STAT signaling (34–37). Moreover, the PD-1/PD-L1 pathway has been implicated in the exhaustion of tumor-infiltrating lymphocytes and an immunosuppressive microenvironment in HL (38).

Initial studies have investigated inhibitors of the PD-1/PD-L1 pathway in the setting of relapsed/refractory HL after autoHCT. In a phase I study of 23 patients with relapsed/refractory HL, including 18 patients relapsed after autoHCT, the anti-PD-1 antibody Nivolumab was associated with a high objective response rate (ORR) of 87%, although complete responses (CR) were infrequent (39). Responses were in general durable.

Subsequent studies with Nivolumab in recurrent HL confirmed high ORRs ranging from 66.3–81.3%, without excessive toxicity (40, 41). Similar results were seen with a second anti-PD-1 antibody, Pembrolizumab (42) (43). On the basis remarkable efficacy anti-PD-1 antibodies in the treatment of HL, including chemorefractory patients and patients progressing after autoHCT, both Nivolumab and Pembrolizumab have now received FDA approval for the treatment of relapsed/refractory HL. However, CR rates with anti-PD-1 monotherapy are low and long-term outcomes are pending. Several studies examining the efficacy and safety of PD-1 inhibitors in combination with other agents, including the anti-CTLA4 antibody Ipilimumab and brentuximab vedotin (BV), are in progress and may further improve outcomes of patients with relapsed or refractory HL. However, autoHCT remains the standard of care for patients with relapsed HL responding to salvage therapy (6).

Non-Hodgkin Lymphoma

Non-Hodgkin Lymphomas (NHL) have variable expression of PD-L1 on the neoplastic cells or in the tumor microenvironment (34, 44–47). Higher PD-L1 expression has been reported in EBV-associated subtypes of NHL, primary mediastinal B-cell lymphoma (PMBCL) and some T cell lymphomas, whereas PD-L1 expression is typically lower in diffuse large B cell lymphomas (DLBCL) and follicular lymphoma (FL) (44). Early studies have shown variable activity of PD-1 inhibitors against NHL subtypes (48). In a phase I cohort-expansion study of 81 patients with relapsed lymphomas, some of whom had undergone autoHCT, Nivolumab monotherapy was associated with ORR of 40% in FL, 36% in DLBCL, 40% in peripheral T cell lymphoma, and 15% in mycosis fungoides patients (49). In patients with relapsed or refractory PMBCL including patients who were treated after autoHCT failure, Pembrolizumab was associated with a promising ORR that was durable for several months, although the study is still ongoing (50). Similarly, in smaller case series, anti-PD-1 inhibitors have demonstrated high efficacy in patients with Richter's transformation of chronic lymphocytic leukemia (CLL) (51), relapsed NK/T cell lymphomas (52), relapsed/refractory primary CNS lymphoma (PCNSL) (53), or mediastinal gray zone lymphoma(54)

The use of PD-1 inhibitors in the treatment of NHL is an area of active investigation and further research is required to determine the optimal combinations and their incorporation in the treatment algorithm (44).

Multiple Myeloma

PD-L1 is highly expressed in neoplastic plasma and MM stromal cells, whereas T cells of MM patients show increased PD-1 expression, suggesting that the PD-1/PD-L1 pathway may play an important role in the immune escape of MM (55–58) and may also lead to development of drug resistance (59). These observations provide the rationale for evaluating checkpoint blockade in MM. Moreover, there is some evidence that the early post- autoHCT setting and associated lymphodepletion may be the optimal timing to evaluate the efficacy of anti-PD-1 inhibitors for the treatment of MM (17, 58).

Nivolumab, however, has shown no single agent activity in MM (60). It has been hypothesized that the apparent lack of efficacy of PD-1 inhibition as monotherapy may be due to the immunosuppressive MM microenvironment (61), or because immunosenescence

rather than exhaustion is the mechanism responsible for T cell dysfunction in MM (62). However, it has also been shown that exhausted/senescent T cells of MM patients may be revived with PD-1 blockade (17). Moreover, immunomodulatory agents, such as lenalidomide, may have potentiating effects in the anti-MM immune responses elicited by anti-PD-1-antibodies (57, 63). Notably, in a phase II trial, Pembrolizumab in combination with Pomalidomide and Dexamethasone was associated with durable responses in 60% of 48 patients with refractory or relapsed MM (64). However the recent halts on studies with Pembrolizumab in MM due to unacceptable toxicities have tempered the enthusiasm for the use of these combinations in MM and more information about the nature of these side effects is awaited.

CHECKPOINT INHIBITION AND ALLOHCT (Table 2)

There is a shared goal of alloHCT and immune checkpoint inhibition in the generation of antitumor immunity through polyclonal activated T cells. In alloHCT, antitumor immunity is mediated by allogeneic T cells that can recognize host antigens on malignant cells. Relapse after alloHCT is associated with donor T cells that become dysfunctional due to exhaustion and can be reinvigorated by PD-1/PD-L1 and CTLA-4 blocking antibodies (65). Evidence from preclinical mouse experiments suggests that immune checkpoint blockade can activate GVL-inducing allogeneic T cells (66, 67).

CTLA-4 inhibition

The anti-CTLA antibody ipilimumab was tested in patients with relapse after alloHCT. An initial trial in 29 patients revealed a favorable toxicity profile of a single infusion of ipilimumab at doses up to 3 mg/kg, and no severe GVHD was observed (68). CR of HL in two patients and partial remission (PR) of mantle cell lymphoma in one patient were observed. A follow-up multicenter trial in 28 patients used multiple doses of ipilimumab (3 mg/kg or 10 mg/kg) (69). Five CRs were observed in the 22 patients receiving a dose of 10 mg/kg, including four patients with extramedullary AML and one with MDS transforming into AML. However, at this dose substantial toxicity was observed, including grade 3 GVHD, 2 severe immune-related adverse events and one death from GVHD with colitis and pneumonitis.

PD-1 inhibition

Checkpoint inhibition with anti-PD-1 antibodies has been reported in two retrospective studies of patients with relapsed lymphoma after alloHCT. In the first study, 20 patients with relapsed HL after alloHCT treated with nivolumab (70). Overall response rates were 95%, but substantial GVHD was observed in six patients (30%), of whom one succumbed to GVHD. In the second study of 31 patients (HL=29, NHL=2) from 10 US centers who underwent treatment with PD-1 inhibitors after alloHCT, the overall response was about 78% at a median of 1.2 year follow up (71). However considerable GVHD was observed, including newly emergent GVHD in 17 (55%) of the patients and 8 (26%) succumbed to GVHD. Checkpoint inhibition with Nivolumab has also been explored in AML. In a case series of three patients with AML who relapsed after alloHCT, Nivolumab led to three

distinct responses: one CR, one disease stabilization and one nonresponse. Pancytopenia and skin GVHD were the only substantial toxicities (72).

The above studies highlight the considerable risks associated with the reinvigoration of GVHD-causing alloreactive T cells with checkpoint inhibition after alloHCT. While checkpoint inhibition has potential effectiveness after alloHCT, further studies are critical to understand which patient populations are more likely to benefit from checkpoint inhibition and the optimal time and dose of treatment to subside the risk of GVHD.

Prior PD-1 inhibition with subsequent alloHCT

With an growing use of immune check point inhibitors in treating lymphomas, increasing numbers of patients referred for alloHCT have previously received therapy with PD-1 blockers. In an international retrospective study of 39 patients (HL=31, NHL=7) treated with an anti-PD1 antibody at some point prior to alloHCT, 38 underwent T cell replete reduced intensity conditioning (RIC) and lower than expected relapse rates were observed. (73). Importantly, while the overall incidences of GVHD were similar to historical controls, the incidence of severe GVHD was substantially higher, and was lethal in 3 patients. Furthermore, prior anti-PD1 treatment did not seem to influence T cell reconstitution but showed a decreased regulatory T cell to conventional T cell ratio. A smaller study of nine HL patients who received Nivolumab as a bridge to allo-HCT also reported GVHD in all the patients (74). These studies suggest a legacy effect of immune check point inhibitors that can reinvigorate allogeneic donor T cells after alloHCT.

CAR T CELL THERAPY AND HCT (Table 3)

AlloHCT and DLI represent the archetypical and most established form of cell therapy in hematological malignancies. However, in recent years, the field of cell therapy has undergone a revolution with the advent of CAR T cells. A CAR is a synthetic fusion protein consisting of the variable portion of an antibody, known as a single chain variable fragment (scFv) that can target an antigen displayed on the surface of a tumor cell, linked to a transmembrane domain TCR CD3 zeta chain, and most commonly co-stimulatory signaling domains from CD28 or 4-1BB (75). The synthetic gene is introduced in the T cell using retroviral or lentiviral vectors that ensure genetic integration and constitutive expression.

The best studied CAR T cells have been those directed against CD19, a 95 kD transmembrane glycoprotein that is normally expressed on mature and precursor B cells (76). It is also expressed on B cell malignancies, including B cell acute lymphocytic leukemia (B-ALL), chronic lymphocytic leukemia (CLL) and NHL (77). Although the expression of CD19 is not exclusive to malignant cells, the elimination of normal B cells is compatible with life, making CD19 a suitable target for B cell malignancies.

The first generation of CAR constructs consisted of the scFv linked to a functional CD3ζ intracellular signaling domain (78). While this initial design was functional (79), effective T cell proliferation and expansion was achieved after the addition of a second-signal transmembrane costimulatory domains that gave rise to the second generation design. Autologous CD19 CAR T cells have been used in relapsed B-ALL with excellent response

rates using both CD28 (80–83) or 4-1BB costimulation (84). CAR T cells have been studied in relapsed/refractory settings, typically in patients who were refractory to chemotherapy or had relapsed after autologous or allogeneic HCT.

CAR T cells and autoHCT

An intense lymphodepleting regimen associated with autoHCT can provide an excellent platform for adoptive T cell therapy (85). In the first trial of CD19 CAR T cells in NHL, two patients with DLBCL received adoptively transferred T cells using first generation construct one month after autoHCT, and one of the two patients remained without evidence of disease nine years later (79). In subsequent trials for lymphoma and CLL, patients received a less intense lymphodepleting regimen, thus alleviating the requirement of stem cell rescue prior to adoptive transfer (86). Of the 15 patients, including nine DLBCL, two indolent lymphomas and four CLL, eight had a CR and four a PR. With more optimized manufacturing of CD19 CAR T cells and adoptive transfer at day 2 post autoHCT, encouraging response rates were achieved (87).

More recently, investigators at MSKCC performed a pilot trial of CD19 CAR T cells post AutoHCT for poor-risk and aggressive B-NHL (NCT01840566). In a preliminary report, the first dose level induced a CR in 4 of 15 patients (88). At a median follow-up for survivors of 31 months, the 2 year PFS was 30% (95% CI: 20-70%) in this high risk population. Given the expected approval of CD19 CAR T cells in patients with DLBCL who are refractory to standard therapy or have relapsed after autoHCT, it is expected that future studies will more closely assess whether CD19 CAR T cell therapies can replace autoHCT entirely in NHL.

CAR T cells and alloHCT

Historically B-ALL in adults has been a poor prognosis disease and patients with relapsed B-ALL have few options of salvage treatment (89). In an initial report of 5 patients with relapsed B-ALL treated with CD19 CAR T cells after high dose cyclophosphamide at MSKCC, minimal residual disease (MRD) negative CR was achieved in all patients, leading to a successful transition to alloHCT (80). Subsequently, the same group reported data in 16 adult patients with relapsed or refractory B-ALL and showed that MRD⁻ CR was achieved in 13 of the patients, and 7 of the 16 (44%) proceeded alloHCT (81). These results are superior to historical controls where salvage therapy could lead to transplant in a minority of patients. Thus CD19 CAR T cells have been shown to be an effective induction agent and bridge to alloHCT (89). In another study, 30 patients with relapsed/refractory B-ALL included 18 patients with relapsed disease after alloHCT, and 27 patients achieved a CR (82). In patients who were ineligible for subsequent transplant, sustained B cell aplasia and detectable CAR T cells were observed, suggesting that, in B-ALL, CD19 CAR T cells can be curative in some patients without a subsequent alloHCT. However relapses, especially with CD19 negative variants have been observed and alloHCT remains an option to induce maximal depth of remission and increase the possibility of cure after CD19 CAR T cell therapy.

Donor CD19 CAR T cells

CAR T cells are unique in their ability to induce specific cytolysis of targets without the requirement for presentation of target peptides in the context of HLA. In the setting of alloHCT, this is an important advantage since the T cells can function and mediate specific killing in HLA-mismatched donor-recipient combinations. Indeed in the phase I trial conducted at MSKCC, four patients were treated after alloHCT relapse with patient-derived “autologous” CD19 CAR T cells that were of donor origin. Two of the treated patients achieved MRD⁻ CR and one had a response with MRD⁺ disease. Despite responses, there was no clinical evidence of GVHD. Similar absence of GVHD was also reported in a patient with adult B-ALL with extramedullary leukemia who received autologous CD19 CAR T cells of donor origin (90).

The lack of GVHD elicited by donor CD19 CAR T cells is intriguing. Donor-derived T cells expressing CD19 CAR can potentially be activated through either the CAR by CD19-target recognition or through the endogenous TCR. It is estimated that about 5-10% of endogenous TCRs can recognize a non-self HLA and hence are alloreactive. These alloreactive T cells are the chief mediators of GVHD. In a mouse model it has been suggested that recognition of CD19⁺ leukemia cells by CD19 CAR T cells promotes an inflammatory response with features of lethal GVHD (91). Thus, in selected genetic backgrounds, alloreactive T cells expressing CD19 CAR T cells may exhibit enhanced activation through CAR activation by CD19 expressing leukemic B cells.

In addition to the two above observations, several clinical studies have shown decreased GVHD mediated by donor T cells expressing a functional CAR. In two reports including 20 patients treated with allogeneic CD19 CAR T cells, 14 of 20 patients had demonstrated prior GVHD and yet did not develop recurrence of GVHD with CD19 CAR T cell infusion (92, 93). In all, 30 patients have been reported who have been treated with allogeneic donor CD19 CAR T cells in the post transplant setting with only 2 patients exhibiting GVHD (90, 92–94). Notably, these studies included patients with active B cell malignancies present at the time of T cell infusion. We investigated this observation in mouse models and found that alloreactive T cells undergo cumulative hyperactivation, and functional exhaustion and deletion in response to persistent signaling through both endogenous (alloreactive) TCRs and (CD19-reactive) CAR (95). The non-alloreactive CD19 CAR T cells undergo normal activation and maintain anti-CD19-immunity leading to tumor clearance. The exhaustion and deletion of alloreactive CD19 CAR T cells is lost when the CD28 costimulation domain in the CAR construct is replaced by 4-1BB costimulation that results in amelioration of exhaustion (96).

The option of donor CD19 CAR T cells for patients who relapse after alloHCT is of great importance since these patients are less likely to have sufficient healthy T cells for CAR T cell generation. Further research into the dynamic interactions between endogenous TCR and CAR is important to design strategies whereby the risk of GVHD is decreased while maintaining the antitumor efficacy of CAR T cells.

Off-the-shelf CAR T cells

Manufacturing of individualized CAR T cells hampers its wider application. Furthermore, both autologous and allogeneic CAR T cell manufacturing is onerous and fails to produce adequate numbers of CAR T cells in a number of patients. Development of a universal donor-derived off-the-shelf CAR T cells that can be applied across HLA barriers could overcome these limitations (97).

In animal models, it has been shown that in vitro generated precursor T cells undergo thymic education in the host upon adoptive transfer leading to the development of tolerance and no GVHD (98). These precursor T cells can in theory be obtained from a non-host, non-donor third party universal donor and transduced with a CD19 CAR for tumor specific activity (99). The development of NOTCH-based OP9-DL1 culture system for generation of precursor T cells has been adapted for use in humans and umbilical cord blood derived precursor T cells can now be generated in vitro (100). This has raised the possibilities of generation of off-the-shelf CAR T cells for clinical use in the near future.

CONCLUSION

In summary, checkpoint inhibitors and adoptive T cell therapies are being integrated into autologous and allogeneic HCT platforms in hematological malignancies, and in some instances, may replace HCT. In many settings, these approaches can be complementary and lead to effective and durable anti-tumor effects. However toxicities due to uncontrolled T cell activation can cause serious and potentially fatal deadly complications. Further research into the strategies to limit toxicities without affecting antitumor immunity is of critical importance.

Acknowledgments

None

FINANCIAL SUPPORT AND SPONSORSHIP

This research was supported in part by National Institutes of Health award numbers P01 CA23766 and NIH/NCI Cancer Center Support Grant P30 CA008748. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. AG is supported by NIH/NCATS Grant #UL1TR00457 administered by the Clinical and Translational Science Center at Weill Cornell Medical Center and MSKCC.

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KEY POINTS

- While scientific rationale supports the notion that peri-autoHCT checkpoint inhibition may lead to enhanced efficacy, high response rates have been observed in both transplant-naïve patients and patients receiving PD-1 inhibitors after HCT failure.
- Checkpoint blockade in the form of anti-CTLA4 or anti-PD-1 antibodies for relapsed hematologic malignancies has shown efficacy after alloHCT; however it is complicated by potentially life-threatening toxicity including GVHD and immune-mediated side effects.
- CD19 CAR T cell therapy is a powerful new treatment option for relapsed/refractor B cell malignancies that can be administered along with autoHCT and/or alloHCT.

Table 1
AutoHCT and checkpoint blockade summary points

1	In phase I and II trials, PD-1 inhibitors have shown high single agents activity in relapsed or refractory HL and in some subtypes of NHL.
2	While scientific rationale supports the notion that peri-autoHCT checkpoint inhibition may lead to enhanced efficacy, high response rates have been observed in both transplant-naïve patients and patients receiving PD-1 inhibitors after HCT failure.
3	CRs with PD-1 inhibitors are infrequent and the available long-term outcome data are sparse; therefore further research is required to determine the optimal incorporation of anti-PD-1 antibodies in the treatment algorithm and whether such agents may replace autoHCT in the future.
4	Outside of clinical trials, autoHCT remains the standard therapy for the management of relapsed/refractory HL, NHL and MM, as outlined in the American Society of Blood and Marrow Transplantation (ASBMT) guidelines.

Table 2
AlloHCT and checkpoint blockade summary points

1	Checkpoint blockade in the form of anti-CTLA4 or anti-PD-1 antibodies for relapsed hematologic malignancies has shown efficacy after alloHCT; however it is complicated by potentially life-threatening toxicity including GVHD and immune-mediated side effects.
2	Administration of checkpoint blockade prior to alloHCT has been associated with higher rates of severe GVHD post alloHCT.
3	Administration of checkpoint inhibitors after alloHCT should be carefully assessed outside the context of a clinical trial, and prior exposure to checkpoint inhibitors should be taken into consideration for patients proceeding to alloHCT.
4	Further research is required in order to determine how to safely incorporate checkpoint inhibitors in alloHCT platforms, and how to identify patients that may benefit from such interventions.

Table 3
CAR T cells and HCT summary points

1	CD19 CAR T cell therapy is a powerful new treatment options for relapsed/refractor B cell malignancies that can be administered along with autoHCT.
2	AlloHCT is a reasonable option for eligible patients who are treated with autologous CD19 CAR T cells for aggressive and intractable B cell malignancies.
3	Adoptively transferred donor CD19 CAR T cells is a viable option to treat patients for relapse after alloHCT.
4	FDA Approval of CD19 CAR T cells for pediatric ALL and adult NHL is expected in the coming months.