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Hematopoietic stem cell transplantation in the era of engineered cell therapy.

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Abstract

Purpose of review: Cellular therapy using T cells modified to express chimeric antigen receptors (CAR-T cells) has had striking success in patients that have failed previous treatment for CD19+ B cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL). Curative therapy for this group of diseases has previously been limited to allogeneic hematopoietic cell transplantation HCT (alloHCT). The recent results of CAR-T cell therapy raise the question of how best to integrate CAR-T cell therapy and alloHCT in the care of these patients.

Recent findings: Within the past 2 years, results from larger trials and increased follow-up of patients treated with CD19 CAR-T cell therapy suggest that some may achieve durable remission without transplant.

Summary: The balance of efficacy and toxicity for CAR-T cell therapy and alloHCT vary by disease type, disease status at the time of treatment, patient characteristics and the specific therapy employed. There are early signals that subsequent transplantation of patients who have achieved remission with CAR-T may be a potentially viable (though expensive) strategy.

Keywords

Cord Blood; Stem Cell Transplant; CAR-T cells; CD-19; CD-20; BCMA

INTRODUCTION

Prior to 2010, allogeneic hematopoietic cell transplant (alloHCT) was the only curative treatment for patients with high-grade lymphoma relapsed after autologous HCT (autoHCT), relapsed acute lymphoblastic leukemia (ALL) and advanced chronic lymphocytic leukemia (CLL). Dramatic reports of the success of chimeric antigen receptor (CAR) T-cell therapy in

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Conflict of Interest

Jacob S. Appelbaum and Filippo Milano declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

treating patients with relapsed or refractory disease(1,2) and the duration of some remissions have raised the possibility that some responding patients may be cured. Six studies presented in the past two years, the Phase II expansion cohort of ZUMA-1(3), the JULIET trial (4), the TRANSCEND trials of JCAR014(5) and JCAR017(6), and trials from University of Pennsylvania(7) and Memorial Sloan Kettering Cancer Center (MSKCC)(8) provide the first measures of long-term efficacy of CAR-T cells in the treatment of aggressive B cell lymphoma (principally DLBCL) and ALL.

These data contributed to the recent FDA approvals for CAR-T cell therapy in the treatment of children and young adults with relapsed/refractory ALL and adults with relapsed/refractory DLBCL. In addition to the FDA approved indications, the availability of clinical trials lead to the consideration of CAR-T cell therapy in patients with B cell malignancies that are either multiply relapsed, refractory to chemo- or immunotherapy, or that have relapsed following alloHCT. The data also create clinical scenarios where both CAR-T therapy and alloHCT could be considered. CAR-T therapy is an attractive option to reduce or eliminate residual disease prior to alloHCT, because CAR-T therapy has low treatment related mortality, and because studies of patients with low or high grade follicular lymphoma (FL) (9), ALL (10–12), Hodgkin's Disease(HD)(13) or DLBCL (14) have consistently shown that transplants performed in the presence of active disease have inferior outcomes and higher rates of relapse.

In this review we begin by addressing whether prior therapies, including alloHCT, impact the safety or efficacy of CAR-T cell therapy. Next, for specific hematologic diseases we review evidence that guide two critical decisions: first, whether to offer CAR-T therapy to patients with residual disease or to proceed directly with alloHCT, and second, given the knowledge that pre-transplant preparative regimens will likely wipe out CAR-T cells, whether to consolidate remissions obtained via CAR-T cell therapy though the use of alloHCT or to delay transplantation until there is evidence of progressive disease. Finally, we review some general factors to consider with regard to initiating transplant or CART cell therapies in patients who are potential transplant candidates.

IMPACT OF PRIOR THERAPY ON CAR-T CELL THERAPY SAFETY AND EFFICACY

The use of CAR-T cell therapy requires *in vitro* expansion of lymphocytes transduced with a gene encoding the CAR protein and infusion of the cell product into patients(15–17). Among patients previously treated with alloHCT, these lymphocytes are derived from the donated stem cell graft. Donor lymphocyte infusion is an effective practice for patients who relapse after alloHCT and have low donor chimerism, but is followed by the development of graft versus host disease (GVHD) in approximately 45% of treated patients(11). Infusion of allogeneic lymphocytes modified with a CAR could also result in GVHD. Surprisingly, in three separate studies of patients with ALL(8,18,19) and an additional study of patients with CLL and B cell lymphoma(20)who had relapsed following alloHCT, none developed GVHD when subsequently treated with CAR-T cells despite the allogeneic origin of the cells. The reason for this difference is not understood. Nonetheless clinical experience shows that the

major toxicities of CAR-T cell therapy, including the cytokine release syndrome and neurotoxicity are not apparently increased by prior allogeneic transplantation(19,21).

Review of recent key clinical trials of CAR-T cells (summarized in TABLE 1) support the hypothesis that there is little, if any, influence of the number of prior lines of chemotherapy or prior use of the bi-specific T cell engager (BiTE), blinatumomab(22), on the success of CAR-T cell therapy. Two potential mechanisms may result in therapeutic resistance: patients may develop immunity to the protein sequence within the CAR binding domain and reject cells expressing CAR protein(19,23), or the shared epitopes may exert strong selective pressure favoring the emergence of antigen-negative tumor variants(24). In the case of ALL, initial findings reported complete remissions (CRs) following treatment with CAR-T cells in two of three patients that had experienced relapses after blinatumomab(18), suggesting that relapse following this CD19 directed antibody therapy does not preclude success of CD19 directed CAR-T cell therapy (though in one of the two patients the remission lasted only 2 months). These data suggest that neither the number of failed prior lines of chemotherapy, nor prior treatment with alloHCT have strong impacts on the outcome of patients treated with CAR-T cell therapy.

SPECIFIC DISEASE CONSIDERATIONS

Acute lymphoblastic leukemia

A complete remission is achieved in approximately 90% of adults with ALL following initial induction chemotherapy(25). European and American expert panels recommend that allogeneic transplantation for adults with ALL be restricted to those in first remission with high risk disease, those that fail to achieve a first remission, or those that suffer a subsequent relapse(26,27). The definition of high risk adult ALL continues to evolve, but generally includes patients who present with a high white blood cell count, who harbor the Philadelphia chromosome (Ph+ disease) or with Ph-like ALL(28). Patients harboring mutations or translocation involving the *mixed lineage leukemia* (MLL) gene, including the t(4;11), may also be a high risk group(29). The persistence of minimal residual disease (MRD), defined as leukemia cells present below the frequency detectable by morphology(30), at the time of allografting, predicts inferior transplant outcomes: in one study, patients who underwent alloHCT in the absence of MRD had a 3 year overall survival of 68% compared to only 40% for those transplanted at a time when MRD was detectable(11). Thus, if HCT is being considered for patients with high-risk ALL in CR1, methods to obtain an MRD-negative CR may improve outcomes(31).

If the decision is made to withhold HCT until after an initial relapse, a challenge then is to get patients back into second remission, since HCT outcomes are superior for patients in CR2 compared to those with refractory relapse. Studies of conventional chemotherapeutic approaches to adult patients with relapsed or recurrent ALL showed CR rates of 20% to 44% (32,33) and median overall survival of 24 weeks(34). However, several newer therapies, including blinatumomab and inotuzumab ozogamycin(35), have recently completed phase III trials showing impressive rates of response in relapsed or refractory ALL. In a phase three trial of 326 patients randomized 2:1 to either inotuzumab ozogamycin or standard chemotherapy, the CR rate was 80.7% with inotuzumab ozogamycin vs 29.4% with standard

chemotherapy(36). In addition, 78.4% of patients with a complete remission were found to be MRD-negative(36) and 41% of patients proceeded to HCT. A similarly designed trial found that blinatumomab resulted in a CR or CR with incomplete count recovery in 44% of patients of whom 76% were MRD-negative(22). Despite these results, the median overall survival of patients treated with blinatumomab was 7.7 months, reinforcing the need for subsequent therapy.

CD19 directed CAR-T cells offer another, perhaps more effective approach for patients with relapsed/recurrent or refractory ALL. A phase I/II trial from MSKCC enrolled 53 adults with ALL(8) obtained CR in 83%, including 67% that were free of MRD. Among 9 patients in whom residual disease remained detectable, all relapsed; while among 32 patients without MRD, 16 patients relapsed. In this cohort, 26 patients achieved a complete remission following CAR-T cell infusion and were followed without further treatment. Nine of these patients remain alive at a median of 29mo of follow up. Among 17 patients who proceeded to HCT, 5 remain alive, 6 relapsed, and 6 died from transplant related toxicities. Comparing outcomes of the 32 patients that achieved a MRD-negative CR following CAR-T cell infusion, no difference in overall survival was seen between patients who completed HCT and those that did not.

A phase I trial at the University of Pennsylvania treated 30 young adults and children with relapsed/refractory ALL with CAR-T and found a CR rate of 90% and a 6 month event free survival rate of 67%(7). As noted above, half of these patients had previously completed an alloHCT. Among 30 patients treated with a defined composition of CD4+ and CD8+ T cells at FHCRC(19), all patients achieved a complete remission when evaluated by bone marrow morphology, and 29 had no evidence of disease by high resolution flow cytometry. At the time of publication 12 of 17 patients (70%) treated with fludarabine plus cyclophosphamide lymphodepletion prior to CAR-T cell infusion remained alive and free of relapse, and 10 completed alloHCT. Overall the rate of alloHCT following CAR-T cell therapy compares favorably to the 24% rate following treatment with blinatumomab(22).

CAR-T cell persistence is one key difference between trials that may impact clinical decision making. The trial at MSKCC, which provides the longest follow-up of ALL patients treated with CART cells found no difference between event-free or overall survival between patients in whom the CART cells persisted for more than or less than 14 days(8). However, cross trial comparisons find shorter persistence of T cells (median 14 days) and higher rates of relapse or death among patients who achieved a MRD negative CR (17 of 26, 58%) among patients reported by Park et al, as compared to patients who achieved a MRD negative CR following treatment with tisagenlecleucel where the median duration of CAR-T persistence was 168 days and the risk of death or relapse by 1 year was only 41%(7). The reason for this difference is not known, but differences in the age of trial participants, manufacturing process, and CAR design, including the costimulatory domains used may be factors. Nevertheless, the observation that some of the patients reported by Park et al. achieved durable complete remissions in the absence of CAR-T cell persistence suggests that ongoing anti-leukemic activity of CAR-T cells may not be required for durable remissions(8,37).

Taken together, the available data on CAR T cells show that they are highly active in adults with recurrent or chemo-resistant ALL, result in a complete remission in most patients, and that a subset of these remissions persist with no further therapy. Thus, there are likely to be several key roles of CAR-T cell therapy for ALL. One is to obtain remissions for patients in first relapse who are refractory or not eligible for other therapies in order to induce a remission prior to allogeneic transplantation. These patients may consider alloHCT as consolidation following successful remission with CAR-T cell therapy. A second possible role is to obtain an MRD-negative first remission in patients who have suboptimal responses to initial chemotherapy. An additional role is for treatment following relapse after alloHCT has failed. Among this population, a second myeloablative transplant is associated with increased toxicity and low success rates(38), but newer preparative regimens may allow this approach to be feasible(39). A central question is whether it will be possible to distinguish those CAR-T cell induced CRs that will persist without further therapy from those that are likely to be short lived. If such a distinction were possible, the toxicities of alloHCT could be avoided in patients who may not require the additional therapy.

High grade B cell lymphoma

Patients with DLBCL who relapse within 1 year after autoHCT or who are refractory to initial therapy have a dismal prognosis. This is well documented in the retrospective SCHOLAR-1 trial(40) in which 861 refractory or relapsed patients had a 26% objective response and a 7% complete response to their next line of therapy. Use of newer agents (venetoclax or ibrutinib) does not significantly improve on this result(41,42). The combination of lenalidomide plus ibrutinib achieved an objective response rate of 44% and a complete response of 14% in a small group of patients(43), but grade 3/4 adverse events occurred in 89% of patients treated and the duration of response has not been reported. Addition of ofatumumab to traditional salvage regimens such as DHAP resulted in a CR rate of 15%, and only 33% of patients completed a subsequent autoHCT(44). These results provide a useful benchmark against which CAR-T cell therapy for DLBCL can be compared.

Given the dismal prognosis of non-transplant approaches to recurrent DLBCL, a number of investigators have explored the use of alloHCT following ablative or reduced intensity conditioning regimens(14,45–47). Similar to ALL, transplants performed for DLBCL in the presence of active disease have inferior outcomes and higher rates of relapse. In the GITMO study of large cell lymphoma(14), pre-transplant disease status was the only variable to remain a significant predictor of outcomes in multivariate analysis (with one-year overall survival being approximately 80%, 60% and 50% for patients transplanted in complete remission, partial remission, and with chemo-refractory disease respectively). Thus, patients most likely to benefit from alloHCT are those with few, if any, comorbidities, and with disease that is in either partial or complete remission.

Three recent key trials of CD19 directed CAR-T products have shown efficacy in diffuse large B cell lymphoma: ZUMA-1(3,48), JULIET(4,49) and TRANSCEND(50). The ZUMA-1 trial was larger (n = 111 patients), and 64% of the enrolled patients with DLBCL had 3 prior lines of chemotherapy, 30% with primary refractory disease(3). All three trials

showed impressive results in this difficult to treat population with manageable toxicity. The JULIET trial is notable for lower CR rates and longer time to infusion, but also allowed the use of bridging chemotherapy. The rate of CR reported from TRANSCEND was 58% among patients treated at dose level 2 (10^8 CART cells), the highest of the three trials. Interestingly, no relationship between the number of prior lines of therapy and response was seen.

A key finding is that PR does not appear to be a meaningful endpoint in this setting: patients that failed to attain a complete response had a median progression-free survival of only 1.9 mo after treatment with axicaptagene ciloluecel(3) and 2.1mo after treatment with lisocaptagene maraleucel(50). In contrast, patients who remain alive and in complete remission 12 months after CAR T cell therapy appear to be at very low risk of relapse. In the case of axicaptagene ciloluecel the number of relapses after 12 months was zero(3). Taken together, these data suggest CAR-T therapy is qualitatively distinct from chemotherapy: with the expectation that roughly 50% of the patients with DLBCL treated with CAR-T will experience a complete remission, and of these approximately 60% will not show progression within the subsequent 12 months and might be cured. Of the 101 patients enrolled in ZUMA-1, only two subsequently completed alloHCT.

When would one consider alloHCT for DLBCL? Cross trial comparisons show similar 1 year survival rates among patients with chemorefractory DLBCL treated with RIC alloHCT or CAR-T cell therapy, however non-relapse mortality (NRM) of CAR-T cell therapy is approximately 3% while NRM associated with alloHCT is ~30%. Thus, the above data provide a strong argument that CAR-T cell therapy supplant alloHCT for patients with chemorefractory DLBCL. In addition, low relapse rates after the first 12 months suggest that a substantial fraction of patients with DLBCL treated with CAR-T cells may be cured. Extrapolating from the GITMO study, one may hypothesize that outcomes could be optimized by targeting alloHCT to patients with responses that are unlikely to prove durable, i.e. patients treated with CAR-T cells who achieved no response or a partial response or patients that achieve a subsequent remission via conventional chemotherapy.

The impact of CAR-T therapy on the outcomes of subsequent transplant is unknown. Thus, to integrate the science of CAR-T cell therapy with transplantation, researchers must identify patients at high risk of relapse following CAR-T. These high-risk patients may have a window of opportunity for good outcomes if offered a RIC alloHCT during CR. In an unselected population of patients treated with CAR-T cell therapy for DLBCL, the toxicity of a subsequent RIC alloHCT for patients in CR would likely outweigh any benefit.

Indolent Non-Hodgkin Lymphoma and CLL

Grades one and two follicular lymphoma (FL), mantle cell lymphoma (MCL) and small/chronic lymphocytic lymphoma (SLL/CLL) represent indolent lymphomas that are frequently responsive to chemotherapy but are unlikely to be cured in the absence of transplantation. AlloHCT is an effective but infrequently used treatment strategy for FL, MCL and CLL because other options have become available. For example, the 5 year survival after relapse of FL treated with salvage combination chemotherapy and autologous stem cell transplantation is nearly 70%(51); the expected 10 year overall survival is

66%(52). Early progression is a poor prognostic factor correlated with historic 5 year overall survival measures near 50%, but recent improvements such as the incorporation of immunomodulatory medications, such as thalidomide and lenalidomide(53,54), and targeted agents(55–57) have improved the outlook of these patients. Mantle cell lymphoma represents a particularly challenging disease, but newer agents have shown some promise(58,59).

Recently, a registry analysis from CIBMTR of patients with FL found that RIC alloHCT resulted in a 5 year progression free survival of 58% and 5 year overall survival of 66%(46), while patients who completed an autoHCT had a 5-year progression free survival of 41%. In a landmark analysis of patients surviving >24 months, the authors report that beyond 2 years after transplant, the early toxicity of alloHCT becomes offset by lower relapse rates translates into an overall survival benefit of alloHCT. Similarly, long term outcomes reported from the German CLL study group describe 10yr overall survival following alloHCT for high risk or refractory CLL of 51%(60).

CAR-T cell therapy is not yet approved by the FDA for treatment indolent lymphomas. Because these tumors tend to be responsive to multiple therapies, short remissions alone provide limited value. Improved long term outcomes, such as matching the 5-year survival of 66% seen from the CIBMTR is a reasonable benchmark. Small trials of CAR-T cell therapy for CLL are encouraging, however the results with low grade lymphoma are mixed. Patients with ibrutinib refractory CLL treated with CAR-T at FHCRC had a CR rate of 71% at four weeks, with 58% having no malignant IGH sequences identified on deep sequencing. The absence of malignant IGH sequences was associated with progression free survival of 100% at a median followup of 6.6 months(61). Treatment of other indolent lymphomas with CAR-T was reported to result in a CR in 2 of 9 patients(6). Thus CLL appears to be particularly responsive to CAR-T. Follicular lymphoma can follow either an indolent or an aggressive course. Among the 23 patients with follicular lymphoma treated with CTL019, the complete response rate was 71% and at a median followup of 28.6mo 70% of patients remained progression free(49). Monitoring a subset of 16 patients with quantitative polymerase chain reaction for CAR-T cell persistence revealed that 8 had loss of CAR-T cells without an associated relapse. This finding, along with the plateau of the progression free survival curve suggests that, similar to the case with DLBCL and CLL, a subset of patients with aggressive follicular lymphoma may be cured by CAR-T cell therapy. Thus, while the option to engage in CAR-T cell therapy for indolent lymphomas and CLL is likely to be dictated by the availability of clinical trials, referral for such a therapy should be considered at the time of relapse following autoHCT or when progression following ibrutinib therapy is seen. This strategy would leave several targeted options (i.e. idelalisib, copanlisib(62) and venetoclax(63,64)) in addition to salvage chemotherapy available for reinduction therapy enabling a possible subsequent alloHCT should the patient relapse after CAR-T cell therapy.

Multiple Myeloma

Myeloma shares key features with CD19+ targets malignancies: a target antigen, B cell maturation antigen (BCMA), has been identified that is highly expressed and mostly limited

to the malignant cell population. As a result, ‘on target, off tumor’ toxicity was expected to be limited, and indeed updated results from recent trials of the bb2121 CAR product showed no instances of dose limiting toxicity or grade 3 neurotoxicity. BCMA CAR-Ts showed modest success in early results of multiply refractory patients, with 2 of 6 patients achieving a CR or VGPR(65). Increasing the CAR-T dose to 150×10^6 cells significantly improved outcomes with ORR rates of 95% in 22 patients(66,67). Responses appear deep: 50% of patients obtained a CR, and 90% of these were negative for MRD. The rate of progression free survival at 9 months was 71%. Importantly, the high cell dose remains associated with a tolerable safety profile. Consideration of BCMA CAR-T cell trials will depend on local availability and will likely be restricted to patients with relapsed/refractory disease. While the above results were limited to patients with high BCMA expression, future trials may expand eligibility, as even low levels of BCMA can trigger CAR T cells *in vitro*(68). A followup data are limited, there is no data regarding transplant following treatment with BCMA CAR-T cells.

Acute Myeloid Leukemia

The challenges of myeloid leukemia set this disease target apart from B cell and plasma malignancies because no single clearly optimal target antigen has been defined. Very few antigens present on leukemic blasts are absent from normal maturing hematopoietic stem cells(69). As a result, CAR-Ts targeted at antigens present on HSCs cells may result in marrow aplasia. Though trials testing CAR-T cells targeting CD33, CD123, mesothelin, Muc1, CD56, CD38, or CD117 individually and in combination are in progress(70), specific challenges exist in engineering CAR-T cells to respond to combinations of target antigens(71). So-called ‘logic gated’ CAR-T cells, which require the presence of two or more antigens, may overcome this limitation by gaining specificity. Early responses of myeloid leukemia to CD33 CART cells have been brief, lasting ~12 weeks(72).

TRANSPLANT FOLLOWING CAR-T CELL THERAPY: THE IMPORTANCE OF CAR-T CELL PERSISTENCE

A key feature of cellular immunotherapy is persistence of the transferred cells. In early studies of CAR-T for chronic lymphocytic leukemia (CLL), those with early cell proliferation and sustained CAR-T cell numbers achieved a complete remission(73), whereas relapses occurred exclusively among patients with loss of the transfused cells. In patients with ALL, Maude et al(7) reported that following infusion, CAR-T cells were detectable for a median of 168 days, along with the expected associated B cell aplasia. Approximately 50% of relapsing patients developed loss of CD19 on their tumor. This supports the hypothesis that ongoing antitumor activity of CAR-T cells likely contributes to the maintenance of remissions in treated patients, and points to the general observation that two major routes of relapse are loss of CAR-T cells or loss of their target antigen on the tumor, i.e. CD19-negative relapse. While followup was brief, among 17 patients treated with fludarabine and cyclophosphamide conditioning, the only patient to relapse with CD19+ disease had completed an alloHCT. The duration of CAR-T cell persistence necessary for a long-term remission in the absence of subsequent alloHCT is unknown and may vary depending on disease type. These data also illustrate that alloHCT following CAR-T therapy

risks effectively trades potentially persistent CAR-T cells that may be responsible for the ongoing maintenance of a remission for a non-specific graft-versus-leukemia effect.

PACE OF DISEASE AND OTHER CONSIDERATIONS

An important detail regarding interpretation of the results of trials of CD19 directed CAR-T therapy lies in the implicit selection criteria imposed by the manufacture of a modified cell therapy product. CAR-T cell therapy requires apheresis of the patient's blood, isolation of circulating T cells, gene transfer, usually with a viral vector, and subsequent expansion in the cell processing facility prior to infusion back into the patient(5). The manufacture times for these products is typically between 2 and 3 weeks. Lymphodepletion prior to modified CAR-T cell infusion is usually delayed until the modified cell product is cleared for clinical use. As a result, patients with rapidly progressing disease may not be able to wait to begin treatment. Reviewing the high rates of production success and infusion without the need for patients to withdraw from trials to receive urgent chemotherapy may suggest that these trials enrolled patients who were both medically fit and could wait several weeks to initiate therapy. This trial design may bias against patients with aggressive disease and improve apparent outcomes relative to a cohort enrolled at presentation (rather than at treatment).

In the future 'intent to treat' trial designs that allow bridging chemotherapy may reduce bias. In addition, improved technologies such as virus-free techniques that rely on DNA transposases are likely to speed manufacture(74,75) and the use of gene-editing techniques to disrupt the endogenous T cell receptor(76) or the use of engineered NK cells(77) may provide a "universal" product available "off the shelf" to patients regardless of matched histocompatibility. These innovations will likely broaden the types of patients who benefit from CAR-T cell therapy.

Recent data suggest that outcomes following use of alternative donor stem cell sources, specifically haploidentical family members(78) and banked cord blood (CB) units(79), are similar to those following transplant with matched unrelated donors. These results have made allogeneic stem cell grafts available for nearly all patients, and therefore donor availability seldom enters into the decision to initially pursue a CAR-T cell approach versus an allogeneic transplant. In the case of the DLBCL, matched related donors were compared to unrelated donors matched at 8 of 8 major histocompatibility loci and no impact of donor type (sibling donor vs. matched unrelated) was found on overall survival(45); similar recent results for patients with ALL were also reported(80). The Italian group found Hodgkin disease patients with an available allogeneic donor had improved survival in comparison to those patients for whom an allogeneic donor was not available(13). However, this cohort did not list patients with available suitable CB units, and only 13% of the patients in the 'donor available' group received an haploidentical HCT.

It is unlikely that patients' other pretreatment characteristics will identify alloHCT or CAR-T cell therapy as a preferred treatment. None of the recent CAR-T cell trials has shown an association between prior treatment (either prior autoHCT, prior alloHCT or the number of prior chemotherapy regimens) and outcome. While patient selection for alloHCT has been increasingly refined through the use of predictive algorithms that can define the likelihood of

non-relapse mortality within the first two years after transplant(81)such algorithms do not yet exist for CAR-T cell therapy, making comparisons between predictive risk scores impossible. Baseline pretreatment factors identified by Sorror et al(81) predict non-relapse mortality associated with both myeloablative and nonmyeloablative alloHCT. These factors can stratify patient groups with probabilities of 2-year overall survival as high as 71% or as low as 34%. However, patients identified as high risk for alloHCT may not have other attractive treatment options, so transplantation, though high risk, may still offer the best chance of both short and long-term survival. Indeed, criteria identifying patients as high risk for alloHCT (principally the presence of organ dysfunction) were also exclusion criteria for several pivotal trials of CAR-T cell therapy(3,4,6,48).

Differences in the characters of risk across the two treatment types may influence patient decision making. Whereas the principle toxicity risk of CAR-T cell therapy is acute(82,83), the longterm morbidity associated with GVHD(84,85) is a unique feature of alloHCT. Thus, it remains challenging to quantitatively compare the risks of alloHCT and CAR-T therapy for individual patients.

CONCLUSIONS

The rapid growth of new treatment options for diseases with historically dismal prognoses (40,58,86) is both exciting and challenging. As these data are new, significant uncertainty remains. The choice to offer HSCT to patients following CAR-T cell therapy relies on historical experience that transplantation has been the only curative option for the subset of patients with relapsed aggressive B cell malignancies. As experience with CAR-T cell therapy grows and long-term remissions prove durable, the use of transplantation may be further refined.

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TABLE 1.

Key Trials of CAR T cells and selected comparisons.

Histology	Setting	CAR-T		Comparison		
		Agent	Notes	CR Rate (%)	Notes	Outcome
DLBCL	Relapsed < 12mo after ASCT or refractory to most recent therapy.	Axicaptagene ciloleucel (3,48)	ZUMA-1 (phase 1/2)	48/92 pts (52%)	SCHOLAR-1 (40)	CR rate = 7%
			Uses CD28 costimulatory domain		Retrospective analysis of 861 pts.	
			Included CD19 negative pts (OR was similar)			OS = 6.3mo
					Nagle et al. (87)	CR rate not reported
		Tisagenlecleucel (4,49)	JULIET (phase 1/2)	Phase 1: 6/14 pts	Retrospective analysis of patients treated at UPENN w/ 1° refractory or relapsed DLBCL post ASCT. (n = 56)	Overall OS = 9.9mo
			Uses 4-1BB costimulatory domain			
			In phase 1, 10 of 38 pts enrolled did not receive CAR-T due to progression or manufacturing challenges	Phase 2: 13/46 pts (30%)		
			No patients subsequently transplanted			progression < 12mo from ASCT OS = 8.8mo
		lisocabtagene maraleucel/ICAR017(50)	TRANSCEND NHL (phase 1/2)	Full Cohort: 13/35pts (37%)		Patients treated w/ alloSCT: OS = 7.2mo
			Uses 4-1BB costimulatory domain			
			Is a defined composition (CD4:CD8 ratio is 1:1)	Dose Level 2: 11/19pts (58%)		
			Trial has several groups and reports both dose level 1 and dose level 2 as well as combined outcomes, with dose level 2 showing a trend toward improved efficacy w/o increased toxicity.		GITMO, MAC and RIC allo-SCT (14)	OS 5 yrs = 39% OS 3 yrs = 42% OS 1 yr = 55% NRM = 28% PFS following transplant = 33%
iNHL	Relapsed/Refractory FL and MCL	FHCRC(6) Tisagenlecleucel (49)	CD4:CD8 = 1, FL/MCL = 10 of 32 pts FL = 15 pts	2/5 FL pts (40%) 11/14 FL pts (71%)	CIBMTR RIC allo-SCT for Gr 1/2 FL(46)	OS 5 yrs = 66%

Histology	Setting	CAR-T			Comparison	
		Agent	Notes	CR Rate (%)	Notes	Outcome
ALL	Relapsed/Refractory ALL	Tisagenlecleucel (7) MDACC (8)	Pts age 3–21, 50% with prior alloHSCT Gr 3/4 AE were 77%, 48% treated w/ tocilizumab. Age > 18. Prior blinatumomab 25%, prior alloHCT 36%.	40/75pts (60%) CR+Cri = 61/75pts (81%) 44/53pts (83%) 67% of CRs were MRD neg.	Inotuzumab ozogamycin(36) Blinatumumab(22)	CR 80.7% vs 29.4% with standard chemo CR 44%. (80% of CRs were MRD neg)
CLL	Relapsed/Refractory after ibrutinib	FHCRC (61)	Defined composition of CD4/CD8 T cells. Some PRs were PET negative.	CR 4/19 pts (21%)	Venetoclax (64) AlloHSCT(60)	CR 8%, PR 52% 10yr OS 51%