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Review

Role of blinatumomab, inotuzumab, and CAR T-cells: Which to choose and how to sequence for patients with relapsed disease

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ABSTRACT

Recent approval of several novel agents has dramatically improved outcomes for patients with relapsed and refractory (R/R) B-cell acute lymphoblastic leukemia. Blinatumomab, a bi-specific T-cell engager targeted to CD3 and CD19, inotuzumab ozogamicin (InO), an antibody-drug conjugate to CD22, and tisagenlecleucel, a CD19 chimeric antigen receptor T-cell with a 4-1BB costimulatory domain, have all demonstrated impressive response rates in R/R B-ALL as compared to historic controls. However, important considerations when choosing among these novel agents include clinical features that may impact efficacy, such as relative disease burden, antigen expression, and T-cell function, as well as patient and disease characteristics that may contribute to risk of toxicity. In addition, suitability of the patient for hematopoietic stem cell transplant (HSCT) as well as patient preference must also be considered. This review will focus on factors to weigh when choosing an agent in the setting of R/R disease and important challenges moving forward.

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Introduction

Historically, survival for adult patients with relapsed and refractory (R/R) acute lymphoblastic leukemia (ALL) has been dismal, with 5-year overall survival (OS) rates of 7% to 8% [1·2]. However, over the past decade, there has been an impressive array of novel agents, which have dramatically changed the treatment approaches and outcomes for patients with R/R B-cell ALL (B-ALL). The 3 currently the United States Food and Drug Administration (FDA)-approved agents, blinatumomab, inotuzumab ozogamicin (InO) and the CD19 chimeric antigen receptor (CAR) T cell, tisagenlecleucel, were all approved within the span of 3 years and all have demonstrated improved response rates and survival as compared to historic controls. Thus, with several excellent treatment options available, choosing which agent to use and how to sequence these treatments can be a challenge. In this review, we discuss some of the important considerations in choosing a regimen, as well as remaining challenges.

Novel Agents

Blinatumomab

Blinatumomab is a bi-specific T-cell engager (BiTE) targeted to CD19 and CD3, which promotes immune mediated elimination of B-cell lymphoblasts by cytotoxic T cells [3,4]. Due to the short half-life, it is administered as a continuous infusion, typically over 4 weeks with a 2 week rest period between cycles. Blinatumomab was initially FDA-approved in 2014 for treatment of adults with Philadelphia chromosome (Ph)-negative relapsed or refractory B-ALL, with expansion to include Ph+ and pediatric ALL in 2017. Recently, blinatumomab received additional approval for MRD-positive disease.

These approvals were based in part on a multicenter phase 2 trial of blinatumomab in 189 patients with Ph-negative primary refractory or relapsed (R/R) ALL, in which 43% achieved a complete response (CR) or CR with partial hematologic recovery (CRh) after 2 cycles of treatment. Impressively, 82% of responding patients also achieved MRD-negativity, defined as less than 10^{-4} detectable blasts [5]. A larger follow-up multi-center randomized phase 3 trial (TOWER) demonstrated similar response rates, with 43.9% of patients achieving CR/CRh or CR with incomplete hematologic recovery (CRi) within the first 2 cycles of treatment, and 76% of responders also with MRD-negativity [6]. Importantly, this

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trial also demonstrated a significantly longer overall survival (OS) with blinatumomab treatment compared to standard of care (7.7 vs 4.0 months, $P = .01$) and longer median duration of remission (7.3 months vs 4.6 months). Similar response rates were seen in Ph+ and pediatric ALL, with CR/CRh rates of 36% and 39%, respectively [7,8].

Inotuzumab ozogamicin

CD22 is highly expressed in most cases of B-ALL, making it an excellent target for immunotherapeutic agents [9]. Inotuzumab ozogamicin (InO) is a potent antibody-drug conjugate (ADC), consisting of a CD22-targeted humanized antibody covalently linked to calicheamicin. Upon binding to surface CD22 on target cells, InO is rapidly internalized and induces DNA damage, leading to tumor cell apoptosis. InO is administered in a fractionated weekly schedule, based on initial phase 1/2 trials demonstrating similar efficacy with decreased toxicity compared to a single dose every 4 weeks [10], and was approved in August 2017 by the FDA for the treatment of adults with first or greater relapse of B-ALL.

The pivotal INO-VATE phase 3 trial for adults with R/R B-ALL randomized patients to InO vs best available intensive chemotherapy (high-dose cytarabine based regimen) [11]. The CR/CRi rate was significantly higher in the InO arm than in the standard therapy arm (73.8% vs 30.9%, $P < .0001$) and, among the patients with CR/CRi, a higher percentage in the InO arm became MRD-negative (78.4% vs 28.1%, $P < .001$). Response rates with InO were similar regardless of duration of prior remission, presence of prior hematopoietic stem cell transplantation (HSCT), salvage attempt, and CD22 expression level (<90% or ≥90% of blasts) [12]. For patients achieving CR/CRi, duration of remission was longer in the InO arm compared to the chemotherapy arm (median, 5.4 months vs 4.2 months $P = .0071$) and patients were more likely to proceed directly to HSCT after achieving CR/CRi (39.6% vs 10.5%; 1-sided $P < .0001$). At long-term follow-up, 2-year OS was increased in the InO arm (22.8% vs 10%, $P = .01$) [13].

Although development of InO in pediatrics has lagged significantly, with the first prospective early phase studies only reported in abstract form in late 2019, response rates thus far appear to be similar to those seen in adult trials, with retrospective and prospective trials demonstrating response rates of 67% to 80% and MRD-negativity rates of 71% to 79% [14,15]. A phase 2 trial (NCT02981628) by the Children's Oncology Group (COG) of 48 patients with multiply refractory R/R B-ALL found a 58.3% CR/CRi rate after cycle 1, with 65.4% of responding patients with MRD <0.01%.

Chimeric antigen receptor (CAR) T cells

CAR T-cells are modified T cells, typically autologous, that have been transduced with a viral vector to express a CAR construct, consisting of an extracellular antigen binding domain fused to an intracellular signaling domain. Binding of the extracellular domain to the target antigen, which is most commonly CD19, leads to T-cell activation [16]. Numerous CAR T-cell products are currently under investigation for both hematologic and solid malignancies and vary in viral vectors, target antigen, and intracellular costimulatory domain (most commonly CD28 or 4-1BB) and, at the time of this writing, 3 CAR T-cell products are currently FDA-approved. The only CAR T-cell product that is currently approved for ALL, tisagenlecleucel (CTL019, Kymriah, Novartis Inc.), is a CD19-targeting CAR containing the 4-1BB costimulatory domain [17] and was granted FDA approval in August 2017 for R/R B-ALL in children and young adults up to age 25 years.

In the initial phase 1/2a single institution trial of tisangenlecleucel a CR rate of 93% was observed in 60 pediatric patients with multiply R/R B-ALL, with relapse-free survival (RFS) of 60% and OS of 79% at 12 months [18,19]. A subsequent phase 2 single-arm, multicenter, global registration trial (ELIANA) enrolled 92 heavily pretreated patients [20]. Seventeen patients were not infused due to CAR T-cell production failure (N = 7) and toxicity or death (N = 10). However, among the 75 treated patients, there were high rates of MRD-negative CR (81%) as well as 12-month RFS (59%) and OS (76%) [21].

Although tisagenlecleucel is the only CAR T product currently FDA-approved for use in B-ALL, several others CD19-directed CAR T products have been studied. Despite variations in the conditioning regimens, patient population, and specific CAR constructs, overall remission rates have remained very good in all of the reported trials, with CR rates ranging from 67% to 93% [18,21-25]. For instance, in a phase 1 trial in 45 children and young adults with R/R B-ALL using a CAR construct similar to tisangenlecleucel, 93% of treated patients achieved an MRD-negative CR, with 89% MRD-negative CR in the intent-to-treat population [22]. Efficacy appears to be relatively similar among adults with R/R B-ALL treated with CAR T-cells. In the largest trial of CAR T-cell therapy in adults, 45 out of 53 (85%) patients with R/R B-ALL achieved MRD-negative CR [24]. Unfortunately, 22 (49%) of the 45 patients who achieved MRD-negative CR relapsed, at a median of 3.5 months (range, 1.1-17.0 months) after CAR T-cell infusion. At a median follow-up of 29 months, the median event-free survival was only 6.1 months, with a median overall survival of 12.9 months.

Considerations in choosing a novel agent

With all 3 novel agents demonstrating impressive response rates, determining the best choice of therapy for patients with R/R B-ALL has become challenging. Outside of a clinical trial, a major consideration is the current FDA-approval for these agents. As of the time of this writing, blinatumomab has the widest approval, with indications for both pediatric and adult patients with relapsed and MRD-positive B-ALL. However, InO is only approved in adult patients with R/R B-ALL, and tisagenlecleucel is only approved for patients up to age 25 years of age with refractory B-ALL or in second or later relapse. Beyond current FDA-approval, there are numerous other considerations, such as efficacy and toxicity, as well as disease- and patient-specific characteristics, which are outlined in Table 1 and described in detail below.

Efficacy

Although efficacy may, at first glance, seem to be the most important consideration in choosing treatment, all 3 of these novel agents have impressive response rates in R/R ALL, with significant improvement in outcome as compared to standard of care. Based on published trials to date, rates of CR/CRi appear to be higher with InO (58%-80%) and CAR T-cells (81%-93%), compared to blinatumomab (36%-44%). However, because of differences in the patient populations and eligibility criteria for these trials, the results cannot be directly compared head to head. For instance, in the large phase 3 trial of InO (INO-VATE), patients in 3rd or later salvage were excluded [11]. This is in contrast to the phase 3 trial of blinatumomab (TOWER), where nearly one-fourth of patients were in 3rd or later salvage [6]. The blinatumomab phase 3 trial also included fewer patients with late relapse (0% vs 43%) and more patients with prior stem cell transplant (35% vs 16%), suggesting that the patients included in the trials of blinatumomab may have been higher risk and may account for some of the differences in response rates. This is further supported by recently published "real world" data from a multicenter retrospective analysis, which found similar rates of CR/CRi with InO and blinatumomab (63% and 65%, respectively) in adult patients with R/R B-ALL [26,27]. Thus, choice of initial treatment for R/R ALL cannot be based on efficacy alone,

Table 1
Comparison of novel agents for treatment of R/R B-ALL.

	Blinatumomab	InO	CAR T
FDA approval	R/R or MRD+ B-ALL Age: any	R/R B-ALL Age: 18+ years	R/R B-ALL Age: <25 years
Efficacy	CR: 36-44% Median OS: 6.1-9.8 mo MRD-neg: 76%	CR: 58-80% Median OS: 5.1-7.7 mo MRD-neg: 78%	CR: 81-93% Median OS: 12.9 mo MRD-neg: 81%
Disease burden	low	low or high	? low
Toxicity	ICANS, CRS Risk: disease burden	SOS Risk: HSCT	ICANS, CRS Risk: disease burden
Prior/current therapy	T-cell dependent ?loss of CD19	Not T-cell dependent Lack/loss of CD22	T-cell dependent Loss of CD19/CD22
CNS efficacy	No	No	Yes
Extramedullary disease	?no	?	?yes
Convenience	Continuous IV infusion x 4 weeks	Short IV infusion weekly x 3 weeks	Delays in start due to manufacturing

CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; HSCT, hematopoietic stem cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; InO, inotuzumab; IV, intravenous; MRD, minimal residual disease; OS, overall survival; R/R, relapsed, refractory; SOS, sinusoidal obstruction syndrome.

as there is not sufficient evidence that efficacy of any one agent is clearly superior to another.

Toxicity

Although generally well-tolerated, the differing toxicities of each agent should be carefully considered. Blinatumomab and CAR T-cell therapy have similar toxicity profiles, mainly consisting of cytokine release syndrome (CRS) and neurologic toxicity. CRS, which results from elevation in inflammatory cytokines, is relatively common with CAR T-cell therapies and perhaps slightly less with blinatumomab. Among patients treated with tisagenlecleucel, 77% experienced some degree of CRS, including 25% with grade 4 CRS [21]. Despite high rates of CRS in the initial dose-finding trials of blinatumomab [28], with current treatment protocols using dose ramp-up and dexamethasone premedication, rates of CRS are significantly lower, with only 4.9% of patients experiencing any degree of CRS in the large phase 3 TOWER trial [6].

Neurologic toxicity is also observed fairly frequently with both CAR T therapy and blinatumomab. In clinical trials of tisagenlecleucel, neurotoxicity was reported in 40% to 45% of patients [21,29]. Termed immune effector cell-associated neurotoxicity syndrome (ICANS), it clinically presents most commonly as encephalopathy, as well as confusion, delirium, hallucinations, aphasia, focal deficits, tremor, somnolence, and less commonly, seizure [29-31]. While not reported with tisagenlecleucel specifically, rare cases of rapid-onset and lethal diffuse cerebral edema have occurred in clinical trials of CAR T-cell therapies [32,33]. Unlike CAR T-cell therapy, no neurotoxicity-related deaths have been observed with blinatumomab, but neurotoxicity remains fairly common, occurring in 9.4% of patients with R/R disease[6] and up to 53% of patients receiving blinatumomab for MRD-positive disease, including 13% with grade 3-4 toxicity [34]. IL-6 receptor blockade with tocilizumab typically results in rapid clinical improvement of CRS following CAR T-cell therapy[35] but unfortunately does not significantly cross the BBB, and patients who have had resolution of CRS after tocilizumab administration can still develop neurotoxicity [36]. Supportive care and corticosteroids are the mainstay of treatment, but whether additional strategies are able to further mitigate toxicity without affecting efficacy is still under investigation.

The most common toxicities reported with InO therapy include myelosuppression, infections, and hepatic toxicity. One of the more concerning toxicities, sinusoidal obstruction syndrome (SOS) was reported in 23 of the 164 patients (14.0%) in the InO arm and in 3 of the 143 patients (2.1%) in the chemotherapy arm on the phase 3 INO-VATE trial [11]. Of note, most of the patients who developed SOS underwent HSCT either before or after treatment with InO; the rate of SOS was low (3%) in patients who did not receive any prior or subsequent HSCT. Similar to the adult experience, in a retrospective multicenter pediatric study, among 21 patients who underwent allogeneic HSCT following InO, 11 (52%) developed SOS, including 2 fatalities [15].

Not all patients develop SOS following InO, and specific risk factors have been identified. In the INO-VATE trial, among patients proceeding to HSCT after InO treatment, the incidence of SOS was greater in older patients (41% vs 17%) [13]. Multivariate analysis found that prior HSCT (odds ratio [OR], 6.02; $P = .032$), conditioning regimens containing dual alkylators (OR 8.61, $P = 0.015$), and last available pre-HSCT bilirubin concentration greater than or equal to the upper limit of normal (OR, 7.08; $P = .011$) were associated with development of SOS. In addition, although not significant in multivariate analysis, there was a trend toward higher SOS rates with increasing number of cycles of InO, with SOS observed in 42% of patients who received 4 to 6 cycles, compared to 19% in patients who received 2 cycles. Based on this data, in patients deemed to be appropriate candidates for InO followed by HSCT, many institutions limit the number of total cycles of InO to 2 or less. Whether this approach sufficiently improves the safety profile in highest risk individuals is still unknown. An ongoing trial is comparing a lower dose of InO to the FDA-approved dosing to determine if this mitigates risk of SOS without compromising efficacy (NCT03677596). Currently, there is no known effective prophylaxis for SOS, although defibrotide and levocarnitine are under investigation (NCT03564678) [37]. Thus, use of InO requires careful consideration of the patient's risk for SOS and close collaboration with the HSCT center regarding conditioning regimen, timing to HSCT, and vigilance for signs and symptoms of SOS with early intervention. In patients deemed high risk for SOS, alternative treatments, such as blinatumomab or CAR T-cell therapy, should be considered.

Burden of disease

One of the many interesting findings that emerged from the initial trials of blinatumomab is that the burden of disease was inversely associated with response to treatment. For instance, in the phase 3 trial of blinatumomab, a lower percentage of baseline bone marrow blasts was associated with increased CR/CRh (65% vs 34.4% for bone marrow blasts <50% or ≥50%, respectively) [6]. The mechanism by which this occurs is unknown, but is thought to perhaps be related to a decreased effector-to-target ratio. The need for a low burden of disease for maximal blinatumomab effect has also been supported by several trials demonstrating higher response rates in the setting of MRD (80-88%) [34,38]. compared to the R/R setting [6].

Based on these studies, it has been suggested that it may be important to achieve at least some degree of cytoreduction prior to introduction of blinatumomab. This strategy was utilized in a Children's Oncology Group (COG) trial AALL1331 (NCT02101853) in which 208 patients age 1 to 30 years with first relapse of B-ALL first received reinduction chemotherapy and then were subsequently randomized to 2 cycles of blinatumomab or intensive chemotherapy [39]. Among patients who were MRD-positive following reinduction chemotherapy, 79% of those treated with blina-

tumomab achieved MRD-negativity (defined as <0.01%), compared to 21% of patients randomized additional cytotoxic chemotherapy.

Data examining the role of disease burden in response to CAR T-cell therapy is conflicting. In the initial phase 1/2a trial of tisagenlecleucel in pediatric patients with multiply R/R B-ALL, responses were observed regardless of marrow disease burden [18,19]. However, in a single institution phase 1 trial of the 19-28z CAR in adult patients, patients with a low disease burden prior to treatment (<5% bone marrow blasts) had significantly longer event-free (10.6 vs 5.3 months, $P = .01$) and overall survival (20.1 vs 12.4 months, $P = .02$), compared to those with a higher disease burden [24]. Regardless, across all studies and CD19 CAR T-cell products, high bone marrow disease burden is associated with an increased risk of severe CRS [40]. In one series, among patients with 50% or greater bone marrow blasts, there was a greater frequency of CRS (41% vs 5%) and neurotoxicity (59% vs 14%) as compared to patients with a lower disease burden [24]. In contrast to blinatumomab and CAR T, the clinical response and toxicity from InO are not related to degree of disease burden [13,41], making InO an attractive choice in patients with significant disease burden.

Antigen expression

Although CD19 is ubiquitously expressed in B-ALL, the degree of antigen expression varies and may be an important predictor in response to CAR T-cell therapy. In a phase 1 trial of 45 children and young adults, bone marrow CD19 antigen load of ≥15% (tumor plus normal B-cells) was significantly associated with duration of B-cell aplasia (hazard ratio 2.99, 95% confidence interval 1.32-9.81; $P < .005$), which is in turn correlated with remission duration. In addition, the magnitude and peak engraftment of CAR T-cells in the peripheral blood was positively correlated with bone marrow CD19 antigen load in the marrow [18]. Interestingly, CD19 antigen load does not appear to be a factor in predicting response to blinatumomab [42] and, thus, in patients with lower CD19 antigen expression, blinatumomab may be preferred.

Because blinatumomab and tisagenlecleucel share a common antigen target, selective pressure from prior treatments must also be considered. CD19-negative relapse is not uncommon following CAR T-cell therapy, occurring in 15 out of 22 (68%) of pediatric patients who relapsed after CR with tisagenlecleucel [21], and 25% to 39% of patients who relapse following an MRD-negative CR [22,24]. This CD19 antigen loss may preclude subsequent therapy with other CD19-directed therapies, such as blinatumomab, and thus must be carefully considered when using CD19-directed CAR T-cell therapies as initial treatment for R/R ALL. Although CD19-negative relapses are significantly less common with blinatumomab (8%-22%) [43,44], some reports have suggested that prior blinatumomab may impair response to subsequent CD19-directed CAR T-cell therapy and increase risk of CD19-negative relapse [45]. However, a retrospective review of 24 adult patients treated with CD19 CAR T-cells did not find an effect of prior blinatumomab on risk of CD19-negative relapse and, in this trial, 4 of 6 patients who received prior blinatumomab achieved an MRD-negative CR [18], suggesting that blinatumomab does not prevent treatment response. Prospective studies are needed, but given the increasing use of blinatumomab in both the frontline and relapse settings, this may be a consideration when sequencing CAR T-cell therapy and blinatumomab

Unlike CD19, not all leukemic blasts express CD22 and only patients with CD22-positive B-ALL were eligible for inclusion in the INO-VATE trial [13]. Thus, InO should only be considered for patients found to have CD22-expression on leukemic blast cell surface, as determined by expert analysis of flow cytometry. However, the precise cut-off for minimal CD22 expression is not known. In the INO-VATE trial, there was no difference in outcomes between patients with CD22 expression on <90% compared to ≥90% of blasts, but only 5 out of 164 (3%) patients had CD22 expression of less than 70%, thus limiting the ability to perform robust subset analysis of patients with lower level CD22 expression. In the COG phase 2 AALL1621 trial, 3 patients had baseline partial CD22 expression (40%, 79% and 83% partial CD22+ populations) and postcycle 1 evaluations revealed emergence of predominantly CD22 negative populations (6.5%, 34%, and 48% CD22+, respectively), precluding eradication of minimal residual disease [46]. In addition, low CD22 antigen density was associated with response to treatment. Patients with *KMT2A*-rearrangement (KMT2A-R) are more likely to have partial CD22 expression and lower antigen density, which may contribute to observed lower response rates in this patient subgroup [47]. Further study is needed to determine minimum necessary levels of CD22 expression, but these findings suggest that CD19-directed treatments should instead be considered for treatment of patients with significant subpopulations of CD22-negative blasts.

CNS and extramedullary disease

One significant benefit of CAR T-cell therapy is the ability to traffic to the CNS, and induce potent and durable responses [48]. In contrast, neither InO or blinatumomab have CNS penetration. In the phase 2 COG trial of single-agent InO in pediatric patients with multiply R/R B-ALL, of the 28 patients who achieved CR/CRi, 2 patients developed progressive disease in the CNS despite CR in the bone marrow [49], highlighting the lack of CNS penetration of InO and need for concurrent CNS-directed therapy. Although there were initial concerns that CNS-directed therapies may worsen the neurotoxicity observed with blinatumomab [34], recent studies have demonstrated that CNS prophylaxis can be administered concurrently with blinatumomab without additional toxicity [8,50]. Thus, in patients with CNS disease, either CAR T-cell therapy should be utilized or CNS-directed therapy added to InO or blinatumomab.

For non-CNS extramedullary disease, there are anecdotal reports of activity of both CAR T-cells and InO [51,52], but data remains fairly limited. In the phase 1/2 study of InO in adults with R/R ALL, although patients with isolated extramedullary disease were excluded, of the 8 patients with concurrent extramedullary disease, 50% had disease regression [53]. In contrast, there is little data to suggest that blinatumomab has activity in extramedullary disease and, in fact, extramedullary relapse appears to be relatively common in some series [42].

Eligibility and need for HSCT

CD19-targeted CAR T-cell therapy has the most compelling data for durable remissions without subsequent consolidation with HSCT. In the phase 2 ELIANA trial, among the 65 patients with CR/CRi, only 8 patients underwent HSCT and responses were ongoing in 29 patients (44.6%) without further therapy, demonstrating that some patients achieved durable remissions without HSCT [20]. In a single institution phase 1 trial of 53 adult patients treated with 19-28z CAR, among the 32 patients who achieved an MRD-negative remission, there was no significant difference in EFS or OS between patients who underwent HSCT and those who did not ($P = .64$ and $P = .89$, respectively) [24]. These results have led to the hope that CAR T-cell therapy may be used as definitive consolidation without HSCT in some patients. However, further research is needed to identify patients who are likely to achieve long-term remission with CAR T-cell therapy alone, and which patients are at higher risk of subsequent relapse for whom consolidation with allogeneic HSCT is warranted. In the initial pediatric phase 1 trial of

tisagenlecleucel, B cell aplasia occurred in all responders, and recovery of peripheral B cells, particularly before 6 months from CAR T-cell infusion, was associated with risk of CD19-positive relapse [21]. Thus, one strategy, particularly in the pediatric setting, is to use CAR T-cell therapy in lieu of HSCT if possible and save HSCT for those who have early B cell recovery or subsequent CD19-negative relapse after CAR T-cell therapy.

Whether patients achieving CR following blinatumomab therapy require HSCT is less clear. In the original study by Topp et al, of 11 patients not receiving HSCT, 6 remained in continued CR at a median follow-up of 31 months [54]. Similarly, in the larger phase 2 trial, 12 of 36 patients (33.3%) without HSCT were alive in continued CR, compared to the 30 of 74 (40.5%) of patients who received HSCT [38]. In contrast, despite the high rates of remission, InO has a short duration of response in most patients, and therefore is typically used as a bridge to definitive therapy, often HSCT. In analysis of pooled data from both the phase 1/2 and phase 3 INO-VATE trials [11,53], 2-year OS was 22.8% for patients receiving InO but increased to 51% among patients proceeding directly to HSCT upon remission [55]. Thus, although patients receiving CAR T-cell therapy, and potentially blinatumomab, may be able to achieve a durable remission without HSCT, patients likely require HSCT to maintain remission following InO therapy.

Logistics/patient preferences

Of the 3 agents, InO has the most straightforward administration, with a short weekly outpatient infusion, which may allow patients the most flexibility with scheduling. Blinatumomab is administered continuously over 4 weeks via an infusion pump, which requires frequent bag changes and continued intravenous access. This, combined with the short period of hospitalization during the initial ramp-up period, may be less convenient for the patient.

CAR T-cell therapy is arguably the most complex of the 3 therapies, requiring a multistep manufacturing process, which can span 4 to 5 weeks. Patients may have difficulty with disease control while awaiting manufacturing and suffer severe complications including infectious death during bridging chemotherapy. In addition, in some cases manufacturing failure or inadequate peripheral T cell count or function may result in lack of CAR T-cell product for infusion. For instance, of the 83 adult patients with R/R B-ALL enrolled in a large CAR T-cell study, 30 did not receive CAR T-cell product [24], highlighting the significant issues of manufacturing. Off-the-shelf allogeneic CAR T-cell products are in development to address some of these issues, but challenges with this approach include risk of graft-versus-host disease and short duration of persistence [56,57].

Future directions and remaining challenges

Sequencing approaches

Many current approaches utilize several novel agents and sequence them in a manner that attempts draw on the relative strengths of each. For instance, in an ongoing cooperative group trial, patients with relapsed B-ALL (or older patients with newly diagnosed B-ALL) will receive one to 2 cycles of InO to decrease disease burden, followed by blinatumomab to maintain remission (NCT03739814). Given the potential risk of sinusoidal obstruction syndrome (SOS) with allogeneic HSCT, CAR T-cell therapy may also have a role as a definitive treatment following InO. As mentioned previously, care must be taken when combining blinatumomab and CD19-directed CAR T-cells, as their common shared antigen may decrease response rates when given sequentially. As CD22-directed CAR T-cells become more common, similar issues will likely arise with InO.

Combination with other agents

Most recently, combination approaches with these novel agents have been used in attempt to improve response rates and duration of remissions. Unlike CAR T-cells and blinatumomab, InO activity does not rely on autologous T-cell function for activity, which allows for concurrent use with cytotoxic chemotherapy regimens. Several ongoing trials are currently investigating this approach and early results have been reported. In a single arm phase 2 trial, 59 adults with relapsed/refractory ALL were treated with the mini-hyper-CVD regimen combined with InO [58]. Overall response rate (ORR) was 78%, with 59% achieving CR, and post-hoc analysis demonstrating superior ORR and OS compared to historic controls. However, 9 patients (15%) developed SOS. Based on the rates of SOS, both protocols were revised to decrease InO dosing from 1.8 mg/m^2 to 1.3 mg/m^2 in cycle 1 and from 1.3 mg/m^2 to 1 mg/m^2 in cycles 2 to 4, with subsequent amendments using a fractionated schedule. Following this amendment, no further cases of SOS were identified. Interestingly, among patients with ALL in first relapse treated with mini-hyper-CVAD plus InO, with or without blinatumomab, 6 patients (13%) achieved a durable MRD-negative remission without subsequent HSCT [59], suggesting this may be a feasible approach for patients who are not transplant eligible. Trials incorporating fractionated InO dosing regimens and combinations with more intensive chemotherapy backbones (ie, hyper-CVAD) are underway (NCT01371630, NCT03488225, NCT01925131).

In contrast, because blinatumomab relies on T cell activity, there is concern that concurrent cytotoxic chemotherapy may decrease the efficacy and thus combination strategies with blinatumomab have relied on immune modulation. For instance, preclinical work suggests that PD-1 inhibition may synergize with blinatumomab [60], and thus ongoing clinical trials are investigating adding PD-1 inhibition and CTLA-4 blockade to blinatumomab treatment in patients with relapsed/refractory ALL (NCT02879695) [61]. Rather than combination approaches, strategies to improve CAR T-cell therapy have, in general, focused on intrinsic modification to the CAR T-cell product. However, some early reports suggest that checkpoint inhibitors may be effectively and safely combined with CAR T-cell therapy to improve efficacy [62] and is currently being studied in ongoing trials (NCT00586391).

Remaining challenges

Despite the impressive progress that these agents have provided in the treatment of R/R B-ALL, several challenges remain. Certain disease subsets, such as *KMT2A*-R B-ALL, appear to have poor response even to the novel agents. Among patients treated with InO, the small subgroup of patients with *KMT2A*-rearrangement (*KMT2A-R*) were less likely have CD22 expression and had the lowest MRD-negative rate and shortest median progression-free survival compared to other cytogenetic subgroups [47,63]. CD19-targeted treatment of *KMT2A* -R B-ALL has been reported to induce lineage switch to acute myeloid leukemia [64-66].

In addition, as these agents are increasingly incorporated into upfront therapy, whether they will retain efficacy in the relapse setting is unknown. With the recent FDA-approval, blinatumomab is now becoming standard of care treatment for any patient with MRD-positive B-ALL. Although InO is not approved in the MRD-setting, a currently ongoing cooperative group trial for adolescents and young adults with newly diagnosed B-cell ALL randomizes patients to receive InO following induction, in attempt to decrease MRD and improve outcomes (NCT03150693). InO is also being studied in newly diagnosed older adults with B-ALL, either

in combination with less-intensive chemotherapy [67] or in combination with blinatumomab, for a "chemotherapy-free" approach (NCT03739814). An ongoing COG trial is investigating the use of tisagenlecleucel in newly diagnosed high risk pediatric and young adult patients with MRD-positive B-ALL following consolidation therapy (NCT038767690). Depending on the results of these trials, it is possible that all 3 of these novel agents will become a standard of care treatment for newly diagnosed patients, which in turn could impact efficacy in the setting of relapse.

Conclusion

In summary, choosing an treatment approach for a patient with R/R B-ALL requires consideration of multiple factors and is not a simple one-size fits all approach. While the approval of these novel agents has made the past decade and exciting time for the field of B-cell ALL and has dramatically improved the outcomes for these patients, now the treatment of R/R B-ALL has become somewhat of an embarrassment of riches, with many good options available. Choosing which agent to use, and when, depends on many factors, including both patient-related and disease-specific considerations. Future studies will be needed to determine how to best combine and sequence these agents so that the best outcomes can be achieved.

Conflict of interest

Dr Curran serves on an advisory board for Servier. Dr O'Brien received an honoraria from Pfizer, as well as research funding to her institution from Pfizer, AbbVie, Amgen, Jazz Pharmaceuticals, and Bristol Meyers Squibb.

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