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# Hematopoietic Cell Transplantation for Lymphoma in the Era of Genetically Engineered Cellular Therapy: It's Not Quite Time to Scrap the Old Vehicle for the New CAR

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## Abstract

**Purpose of the Review:** Second-line platinum-based salvage chemotherapy followed by high-dose chemotherapy and autologous hematopoietic cell transplantation (AHCT) has remained the standard of care (SOC) for relapsed and primary refractory (r/r) DLBCL for greater than 2 decades. In the post-rituximab era, this strategy has yielded disappointing outcomes for r/r patients with curability in less one-quarter of the patients by intention-to-treat.

**Recent Findings:** Given the FDA approval of CAR modified T cells directed against CD19 (CD19 CAR T) for DLBCL following 2 lines of therapy and/or failed AHCT, encouragement with this therapy in the second line for r/r patients has naturally prompted randomized phase III studies against the aforementioned SOC. The predominant hurdle to procession to AHCT is chemotherapy sensitivity after platinum-based salvage therapy.

**Summary:** In this review, we will discuss recent investigations to improve response rates in r/r DLBCL with the intent of proceeding to potentially curative AHCT, as well as investigations to decrease progression post-AHCT. Additionally, data regarding currently FDA approved CD19 CAR T cells will be reviewed. Within 2–3 years, we will know if the multicenter/multinational studies of CD19 CAR T will replace SOC salvage therapy and AHCT in the second-line. The role of allogeneic HCT will also be briefly reviewed in the context of these therapies.

### Keywords

DLBCL; Autologous Hematopoietic Cell Transplantation; CAR modified T cells; Allogeneic Hematopoietic Cell Transplantation

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Conflicts of Interest:

M.S. has served as a paid consultant for McKinsey & Company and Angiocrine Bioscience, Inc. C.S.S. has served as a paid consultant on advisory boards for: Juno Therapeutics, Sanofi-Genzyme, Spectrum Pharmaceuticals, Novartis, Precision Biosciences, Kite, a Gilead Company, and GSK. He has received research funds for investigator-initiated trials from: Juno Therapeutics and Sanofi-Genzyme. R.L. has no conflicts of interest.

## Introduction:

### Standard of care for relapsed or primary refractory DLBCL

The treatment landscape for relapsed diffuse large B cell lymphoma (DLBCL) continues to rapidly evolve with the advent of CD19-directed chimeric antigen receptor T cell (CAR T) cells. There is considerable optimism given favorable results with CAR T cells thus far, and many have understandably begun to question whether these genetically modified products will ultimately alter decades-old treatment paradigms. In 1995, the PARMA study demonstrated an overall survival benefit that set the enduring standard for consolidation with high-dose therapy and autologous hematopoietic cell transplantation (AHCT) in physiologically appropriate patients with relapsed or primary refractory (r/r), aggressive B cell non-Hodgkin lymphomas (NHL).(1) Today, the crucial prognostic variable of success after consolidative AHCT remains the demonstration of chemosensitivity by functional imaging after second-line therapy.(2–7) The achievement of chemosensitivity is reliant upon appropriate platinum-based salvage immuno-chemotherapy. The phase III, randomized, CORAL study compared the salvage regimens, R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) and R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin), noting overall similar response rates prior to AHCT and similar progression-free (PFS) and overall survival (OS) for both cohorts after AHCT.(8) Post-hoc analysis according to cell-of-origin revealed superior PFS for germinal center B cell like DLBCL treated with R-DHAP.(9) Other platinum-based salvage regimens have been prospectively studied, ultimately resulting in chemosensitivity for about 50% of transplantation-eligible patients with no difference in overall response rate between regimens included in the CORAL and the NCIC-CTG LY.12 study.(8,10) Many groups have investigated modifications to the platinum-containing salvage backbone with limited success. In a multicenter, randomized study, substitution of rituximab with an alternate anti-CD20 monoclonal antibody, ofatumumab, showed no improvement in outcomes.(11) R-ICE combined with the humanized anti-CD40 monoclonal antibody, dacetuzumab, was compared against R-ICE in a randomized, placebo-controlled phase 2b study though enrollment was stopped due to futility.(12) The addition of novel agents such as lenalidomide and vorinostat have led to modest efficacy in early phase studies.(13,14) Our group recently reported a promising overall response rate in a phase I study that combined R-ICE with the Bruton tyrosine kinase inhibitor, ibrutinib, in patients with DLBCL prior to planned AHCT, particularly in patients with non-germinal center cell of origin phenotype.(15)

### Improvements in AHCT in the Modern Era

Moreover, efforts have been made to improve upon rates of durable remissions by modifying myeloablative conditioning regimens for patients that proceed to AHCT. The BMT Clinical Trial Network 0401 study compared the standard rituximab/BEAM (carmustine, etoposide, cytarabine, and melphalan) with the radioimmunotherapy agent, Bexxar, plus BEAM with disappointing results.(16) Others have tested modifications to conditioning regimens in single-center and early phase studies, but the most commonly utilized regimen prior to AHCT remains BEAM, with a PFS and OS of about 50% at 3-years post-AHCT in patients with DLBCL.(17)

Historically, because of the dose intensity of myeloablative conditioning chemotherapy prior to AHCT, older patients were often excluded from AHCT studies.(18) While no strict guidelines regarding the appropriateness of AHCT for an individual have been established, commonly accepted criteria include a disease-related indication, adequate functional status and organ function, sufficient psychosocial and financial support; and most importantly, chemosensitivity to salvage therapy.(19) Age cutoffs for AHCT eligibility criteria remain controversial. While AHCT is offered primarily to patients < 65 years-old in many European countries, there is no such upper age limit in the United States and the Centers for Medicare and Medicaid Services reimburses for AHCT in patients who are < 78 years-old.(19) Increasingly, individual "physiologic age" and functional reserve, determined by a comprehensive geriatric assessment, are used to guide AHCT decision-making and dose modification of the conditioning regimen.(20) Moreover, given the profound disease-related constitutional symptoms of aggressive lymphomas and their functional impact, it is not uncommon for an ineligible patient to become eligible after responding to salvage therapy.

Several recent studies illustrate the successful use of AHCT in older lymphoma patients. A nationwide Japanese retrospective study identified 484 older adults (≥ 60 years) who underwent AHCT for (r/r) DLBCL. Two-year PFS and OS were 48% and 58%, respectively.(21) In a subgroup analysis of the phase III CCTG LY.12 trial for r/r aggressive lymphoma receiving salvage immuno-chemotherapy followed by AHCT, older patients (> 60 years) had similar rates of febrile neutropenia and adverse events requiring hospitalization than the younger patients. There were no significant differences in 4-year OS (36% and 40%), though 100-day non-relapse mortality (NRM) was higher in older transplanted patients, 8.06% versus 1.85%.(22) In contrast, our group's retrospective analysis of 202 NHL patients (≥ 60 years) who underwent BEAM-conditioned AHCT demonstrated a NRM incidence of 4% at 100 days and 1-year post AHCT, and 3-year PFS and OS of 60% and 73%, respectively, both comparable to younger historical cohorts.(23) Finally, a retrospective analysis of 170 NHL older patients (≥70 years) who underwent AHCT resulted in 2-year PFS, OS, and NRM estimates of 58%, 65%, and 7%, respectively.(24) Taken together, these studies suggest that age alone should not be used as AHCT eligibility criteria, and that AHCT can achieve favorable outcomes in older patients. There will be a proportion of older and frail patients who are not eligible for AHCT because of geriatric impairments, comorbidities, disease refractoriness, or patient preferences. Treatment options for these patients many include conventional chemotherapy at reduced dose, clinical trials, radiotherapy, and optimal supportive care. Recently, several well-tolerated, effective regimens have been reported including R-GemOx (rituximab, gemcitabine, and oxaliplatin), R-Bendamustine, and lenalidomide with rituximab.(25–27) These regimens generally produce an overall response rate of 30–60% with favorable toxicity profiles. It is crucial to reassess AHCT eligibility if these patients achieve a chemosensitive remission.

## The Emergence of CD19 CAR T Cell Therapy

While the transplantation field continues to improve upon standard of care AHCT, CD19 CAR T cell therapy has quickly emerged as a potential competitor in the r/r B cell NHL space. Since late 2017, the Food and Drug Administration has approved two commercially available products, axicabtagene ciloleucel (Yescarta®, Kite) and tisagenlecleucel

(Kymriah®, Novartis), for the treatment of patients with multiply r/r B cell NHL who had disease progression after AHCT or whose disease was refractory despite pre-AHCT salvage therapy. The first commercially available CAR T product in the US, axicabatagene ciloleucel, was approved based on the multicenter, phase II ZUMA-1 study that demonstrated an objective response and complete response (CR) rate, respectively, of 82% and 54% at a follow-up of 15.4 patients in heavily pre-treated patients, 73% of whom had DLBCL.(28) Tisagenlecleucel, was approved based on the multicenter, phase II JULIET that demonstrated overall response and CR rates, respectively, of 52% and 40%, in the 93 patients treated with a median follow-up of 14 months. It is important to acknowledge the unique adverse event profiles of both commercially available products that include cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS).(29,30) Moreover, three patients on the ZUMA-1 study died during treatment while no deaths were attributable to CAR T cell treatment on the JULIET study. Recent longer-term updates of the ZUMA-1 and JULIET studies have been presented in abstract form at the Transplantation and Cellular Therapies Annual Meeting 2019, demonstrating overall favorable and durable results. However, these data should be interpreted with some caution as they were not analyzed by intention-to-treat as was done in the pivotal CORAL study.(8,31,32)

Naturally, these favorable response rates in the r/r settings have led groups to investigate whether CD19 CAR T cells may improve the clinical outcomes for patients who are considered ineligible for AHCT based on older age or chemorefractory disease.(33) The ZUMA-1 and JULIET studies have only variably included patients aged ≥ 65 years old (17–24%).(34) In an FDA-pooled analysis of patients treated on two prospective CAR T-cell trials (N=214), overall similar rates of CRS and grade ≥ 2 CRS were observed in patients < 65 years old as compared to patients ≥ 65 years of age. There appears to be an overall higher incidence of ICANS in older patients.(35) Similar analysis from the ZUMA-1 trial has found comparable response rates at day 30 between the two groups. Importantly, grade ≥ 3 CRS, grade ≥ 3 neurotoxicity, and median length of hospitalization were all comparable.(36) While patients in these studies were not stratified by geriatric impairment, these results suggest that CD19 CAR T cell therapy may also be an effective and safe approach for selected older, vulnerable patients with r/r aggressive B cell NHL and warrants perspective evaluation. Table 1 provides a basic comparison of autologous HCT and CD19 CAR T cells in r/r B cell NHL to date.

The eagerly awaited results of currently accruing pivotal studies may transform the standard of care for r/r DLBCL set by the PARMA study in 1995 (Table 2). In ZUMA-7, patients will be randomized to receive axicabtagene ciloleucel or second line platinum-based salvage therapy followed by consolidative AHCT in chemosensitve patients (NCT03391466). In a similarly designed phase III study, BELINDA, patients will be randomized to platinum-based salvage therapy followed by tisagenleucel or to platinum-based salvage therapy followed by consolidative AHCT (NCT03570892). The TRANSFORM study is a randomized, open-label, multicenter clinical trial in which patients will be randomized to physicians' choice standard of care salvage therapy prior to AHCT in chemosensitive patients versus lymphodepleting chemotherapy followed by infusion with JCAR017, or lisocabtagene maraleucel (NCT03575351). It should be noted that patients with primary or

secondary central nervous system lymphoma (CNSL), which is typically of DLBCL histology, have decidedly benefited from consolidative AHCT in first or subsequent relapses with durable remission rates exceeding 80% in several series even in patients >65 years-old. While responses to CD19 CAR T cell therapy have been reported in CNSL, this modality remains an experimental approach for these patients given concerns for inducing severe neurotoxicity.(37)

Patients who are ineligible for or whose disease progresses after AHCT can be considered for allogeneic (allo) HCT, a modality with the added benefit of a graft-versus-lymphoma effect that produces in durable remissions in about 30–40% of patients with r/r B cell NHL, even those with aggressive disease biology and older patients.(38–43) The approval of CD19 CAR T cell therapy has complicated the decision of where to sequence allo-HCT, particularly given the historical rates of NRM associated with this approach.(44) Moreover, whether patients that achieve CR after CAR T cell therapy should proceed to consolidative allo-HCT remains unknown and requires systematic inquiry. At our center, patients that achieve a CR by functional imaging at 1-month post CAR T cell therapy are generally maintained on active surveillance. If a patient remains in CR at the 3-month mark, a favorable marker of potential durable disease control based, he or she will be maintained on typical active surveillance as guided by their clinical scenario.(31) The more complex question arises when a patient has achieved a partial remission (PR) at 1 month, as a proportion of these patients may convert to CR by 3 months post-CAR T cell. For this unique group of patients, our general practice remains active work-up of potential donors and allo-HCT strategy to be adequately prepared for possible allo-HCT should the patient's disease progress (and remission can be re-achieved). This type of approach requires a coordinated multidisciplinary effort between institutional services, particularly given that HCT experts often administer CAR T cell therapy at many centers.

## Conclusion:

The HCT field has evolved over the years with improvements in overall outcomes across disease histologies. Similarly, enhancements in the safety and efficacy of CAR T cell therapies and other cellular therapies will continue to enrich the field. We eagerly await the results of randomized studies that will help answer the question of whether CD19 CAR T cells may be superior to AHCT. Until those data emerge, AHCT remains the standard of care in patients with rel/ref aggressive B cell NHL in second remission. Additionally, allo-HCT should be considered in patients experiencing progression after AHCT or after CAR T cell therapy.

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**Key Points:**

- Salvage immune-chemotherapy followed by autologous hematopoietic cell transplantation (AHCT) remains the standard of care for relapsed, refractory DLBCL.
- AHCT outcomes have improved over the years and is a viable option for physiologically appropriate patients > 70 years old.
- CD19 CAR T cell therapy has shown effective and durable responses in a subset of relapsed, refractory DLBCL patients.
- The outcomes of multicenter, randomized studies of AHCT versus CAR T cell therapy may define new standards of care.

**Table 1.**

Comparison of Autologous HCT and CD19 CAR T Cells in R/R B Cell NHL to Date

| | Autologous HCT | CD19 CAR T Cells |
|---|---|---|
| **Collection & Manufacturing** | • Stem cell mobilization required prior to collection<br>• No cell engineering required | • No mobilization required, but need adequate ALC<br>• Cell engineering over days to weeks |
| **Insurance Approval** | • Rapid; considered standard of care | • Days to weeks; carrier dependent |
| **Patient Factors** | • Chemosensitivity to salvage therapy required<br>• Well-validated tools to estimate risk of NRM (e.g., HCT-CI)(45)<br>• NRM <5% in modern era, even in older patients | • Chemosensitivity to salvage or bridging therapy not required<br>• No well-validated tools to estimate risk of NRM<br>• NRM not yet well-defined, but upwards of 7%(31) |
| **Conditioning** | • Relies on myeloablative chemotherapy +/− radiation | • Relies on lymphodepletion, not dose intensity |
| **Toxicities** | • Defined by early regimen-related toxicities (mucositis, nausea/vomiting, infections, etc.)<br>• Very low risk of CRS, immune-mediated complications, and neurologic toxicity<br>• Late toxicities include prolonged B cell aplasia, risk of secondary malignancies, etc. | • Defined by CRS and ICANS<br>• Early, prolonged cytopenias common<br>• Late toxicities not yet well-defined, but include prolonged B cell aplasia |
| **Pivotal Studies to Date** | • Randomized, multicenter phase III studies analyzed by intention-to-treat | • Multicenter phase II studies, not analyzed by intention-to-treat |

ALC, absolute lymphocyte count; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell associated neurotoxicity syndrome; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation comorbidity index; NHL, non Hodgkin lymphoma; NRM, non-relapse mortality; R/R, relapsed/refractory

**Table 2.**

Active Randomized Clinical Trials Comparing AHCT versus CAR T Cells

| Clinical Trial | Design | Primary Outcome |
|---|---|---|
| **ZUMA-7** (NCT03391466)<br>Sponsor: Kite, A Gilead Company | **Arm A (SOC)**: Investigator's choice platinum-based salvage followed by AHCT<br>**Arm B (Experimental)**: Lymphodepleting chemotherapy followed by axicabtagene ciloleucel | Event-free survival |
| **BELINDA** (NCT03570892)<br>Sponsor: Novartis | **Arm A (SOC)**: Investigator's choice platinum-based salvage followed by AHCT<br>**Arm B (Experimental)**: Investigator's choice of optional platinum-based salvage followed by lymphodepleting chemotherapy followed by tisagenleucel | Event-free survival |
| **TRANSFORM** (NCT03575351)<br>Sponsor: Celgene | **Arm A (SOC)**: R-DHAP, R-ICE, or R-GDP followed by AHCT<br>**Arm B**: Lymphodepleting chemotherapy followed by lisocabtagene maraleucel | Event-free survival |

AHCT, autologous hematopoietic cell transplantation; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; R-GDP, rituximab, gemcitabine, dexamethasone, cisplatin; SOC, standard of care