Advances and Controversies in
Hematopoietic Transplantation and Cell Therapy
Series Editors: Syed A. Abutalib · James O. Armitage

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Catherine Bollard *Editors*

Cell and Gene Therapies

Springer

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Each volume will focus on different aspects of blood and marrow transplantation or cellular therapy and presents up-to-date data and concepts as well as controversial aspects.

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Historical Perspective and Current Focus

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Miguel-Angel Perales and Catherine Bollard

In the beginning days of blood banking, surgeons would call imperiously for "fresh whole blood" recognizing its superior restorative properties over banked blood. Since then technological advances have made it possible to break down the therapeutic elements of fresh blood into their constituent platelets, red cells, plasma, and clotting factors, and through apheresis, blood bankers can even provide granulocytes, lymphocytes, progenitors, and stem cells. The component therapy concept is so widely accepted that we cease to think it as being unusual. Curiously, and in contrast, transplant physicians have been slower to apply a component therapy approach to their practice. Even today the majority of hematopoietic cell transplantation (HCT), whether from the bone marrow, peripheral blood, or cord blood, is as unmanipulated as the "fresh whole blood" beloved of our surgeons of the past. Nevertheless, the attractions of a component therapy approach to HCT are many including but not limited to (1) T-cell depletion by selection of $CD34^+$ cells, which can reduce GvHD, and (2) infused donor lymphocytes which can improve engraftment and treat leukemic relapse. Careful studies in the 1990s determined the doses

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of $CD34^+$ cells and lymphocytes in the graft that led to the best outcomes, and donor lymphocyte infusion doses were calibrated to achieve graft-versus-leukemia effects with minimal graft-versus-host disease.

These initial graft manipulations contributed to steady progress to improving HCT outcome, extending the upper age limit of HCT recipients and paving the way for successful transplants from HLA-haploidentical mismatch donors. However, we now see these advances as merely a prelude to the full realization of the component therapy approach through modern cell and gene therapies. Advances in technology in translational research have opened up exciting and powerful new cell-based treatments which promise to dramatically transform the way we perform allogeneic HCT and eliminate the obstacles of GvHD, relapse, and transplant-related mortality (TRM).

In this volume, we review the exciting developments in cell and gene therapy as it relates to HCT. From blood or marrow, a diverse repertoire of cell products are now manufactured including mesenchymal stromal cells (Chap. 12), dendritic cell vaccines (Chap. 11), and NK cells (Chap. 10). Gene-modified T cells can potentially control GvHD through inserted suicide genes. T cells can be targeted to neoplastic cells by transducing them with chimeric antigen receptors (CAR T cells) or artificial receptors (α/β TCRs) (Chaps. 2, 3, 4, 5, 6, and 7). The ultimate goal of cell and gene therapy is to provide remedies for all the major obstacles to successful outcomes of HCT. Regulatory T-cell (Chap. 9) or mesenchymal stromal cell infusions aim to prevent or treat GvHD. Tumor antigen-specific T cells, CAR T cells, α/β TCR T cells, and NK cells can prevent or treat leukemic relapse, and T cells targeting multiple viruses (Chap. 8) can reduce transplant morbidity and mortality. Finally, gene therapy is being used not only in malignant but also in nonmalignant hematologic disorders (Chaps. 13 and 14).

With the rapid advances in treatments of neoplastic disease and the prospect of continuing breakthroughs in treatments, as we have seen with the introduction of tyrosine kinase inhibitors and recently checkpoint inhibitors, we should be wary about predicting where HCT will be by the next decade. However, the rapid advances in cell therapy show a growing ability to render HCT safer and more effective. The progress documented with cell and gene therapy ensures that HCT will continue to remain central to the treatment of neoplastic and nonmalignant disorders for the foreseeable future.

Most Recent Clinical Advances in CAR T Cell and Gene Therapy 2017/2018

2

Syed A. Abutalib and Saar I. Gill

2.1 Introduction

Adoptive cell therapy with gene-engineered T cells bearing antitumor-reactive T-cell receptor or chimeric antigen receptor (CAR) is a promising and rapidly evolving field of translational medicine. This approach has delivered exciting responses for some patients with lymphoid hematologic neoplasms, leading to recent US Food and Drug Administration approvals. Hematopoietic stem cellular gene therapy has also shown promising advances, with durable and potentially curative clinical benefit and without the potential toxicities of allogeneic hematopoietic cell transplant. However, for both of these novel strategies, many questions remain unanswered. Compared to synthetic viral gene addition therapy (e.g., CAR T-cell engineering), translation of gene-editing technologies to patient care is in its infancy. Multiple clinical trials are ongoing or expected to open for CAR T cell and inherited monogenic disorders (Gardner et al. 2017) (refer to subsequent disease-specific chapters in the book). In this chapter, we will highlight the most recent and clinically relevant developments in the arena of gene-modified T-cell-based therapies and hematopoietic stem cellular gene therapy specifically focusing on hematologic disorders. We will conclude the chapter by summarizing the apparent challenges and directions for the future.

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2.2 Relapsed/Refractory B-Lineage Acute Lymphoblastic Leukemia

2.2.1 Children and Young Adults: CAR T Cells Show Promising Results

Transitioning CD19-directed CAR T cells from early-phase trials to a viable therapeutic approach with predictable efficacy and low toxicity for broad application is currently complicated by product heterogeneity resulting from (a) transduction of T cell of undefined subset composition, (b) variable efficiency of transgene expression, and (c) the effect of ex vivo culture on the differentiation state of the manufactured cells (Gardner et al. 2017; Rouce and Heslop 2017). Gardner et al. (2017) enrolled 45 children and young adults in PLAT-02 phase I trial with $CD19^+$ relapsed or refractory B-lineage acute lymphoblastic leukemia (ALL). They used CD19 CAR product of defined $CD4^+/CD8^+$ (1:1 ratio) composition with uniform CAR expression and limited effector differentiation (described later). The rationale for this strategy comes from preclinical studies that suggest that a 1:1 ratio of $CD4^+$ to $CD8^+$ cells and culture with appropriate homeostatic cytokines would ensure maximum effectiveness of both T-cell subsets and would yield a less terminally differentiated T-cell population with maximum tumor killing capacity, prolonged CAR T-cell persistence, and the ability to retain memory and self-renewal capacity (Gardner et al. 2017; Rouce and Heslop 2017; Riddell et al. 2014). Products meeting all defined specifications could be manufactured in 93% of enrolled patients. The maximum tolerated dose (MTD) was $1x10^6$ CAR T cells/kg (doses ranged from 0.5 to 10×10^6 cells/kg), and there were no deaths or instances of cerebral edema attributable to the product toxicity. The overall intent-to-treat minimal residual disease-negative (MRD-negative) remission rate was 89%. The MRD-negative remission rate was 93% in all patients who received a CAR T-cell product and 100% in the subset of patients who received fludarabine (Flu) and cyclophosphamide (Cy) lymphodepletion. Twenty-three percent of patients developed reversible CRS and/or reversible but severe neurotoxicity. No deaths resulting from toxicities were reported. These data demonstrate that manufacturing a defined composition CD19 CAR T cell identifies an optimal cell dose with highly potent antitumor activity and a tolerable adverse effect (AEs) profile in a cohort of patients with an otherwise poor prognosis. This manufacturing platform therefore provides a significant advantage over prior reported trials (see Chaps. 4 and 5). The observation that 100% of patients receiving Flu/Cy lymphodepletion had an MRD-negative remission further reinforces the importance of lymphodepletion regimens that include Flu, as opposed to Cy alone (Gardner et al. 2017; Turtle et al. 2016) (see Chap. 4).

2.2.2 Children and Young Adults: Tisagenlecleucel (CTL019) and Its US FDA Approval[1] (2017)

On August 30, 2017, the US FDA granted approval to tisagenlecleucel for the treatment of patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse (see footnote 1). Approval of tisagenlecleucel was based on a phase II single-arm trial (ELIANA; NCT02435849) of 63 patients with relapsed or refractory pediatric precursor B-cell ALL, including 35 patients who had a prior hematopoietic cell transplantation (Buechner et al. 2017). Median age of the participants was 12 years (range, 3–23 years). Noteworthy, during the presentation of updated results of this global multicenter ELIANA trial at European Hematology Association (EHA®) 2017, it was reported that as of November 2016, 88 patients were enrolled. There were seven (8%) manufacturing failures, nine (10%) patients were not infused due to death or AEs, and four patients (5%) were pending infusion at the time of data cutoff. All patients received a single dose of tisagenlecleucel intravenously within 2–14 days following the completion of lymphodepleting chemotherapy. Of the 63 patients who were evaluable for efficacy, the confirmed overall remission rate as assessed by independent central review was 82.5% (95% CI 70.9, 91.0), consisting of 63% of patients with complete remission (CR) and 19% with CR with incomplete hematological recovery (CRi). All patients with a confirmed CR or CRi were MRD-negative by flow cytometry (FC) method. Median remission duration was not reached (range: 1.2 to 14.1+ months). Grade III or IV AEs were noted in 84% of patients. Serious adverse reactions such as CRS, including fatal CRS and CRS-associated disseminated intravascular coagulation with intracranial hemorrhage, prolonged cytopenias, infection, cardiac failure, and cardiac arrest occurred in patients receiving tisagenlecleucel. FDA approved tisagenlecleucel with a Risk Evaluation and Mitigation Strategy (see footnote 1). The recommended tisagenlecleucel dose is one infusion of $0.2–5.0 \times 10^6$ (CAR)-positive viable T cells/kg body weight intravenously for patients who are less than or equal to 50 kg and $0.1–2.5 \times 10^8$ total CAR-positive viable T cells intravenously for patients who are >50 kg, administered 2–14 days after lymphodepleting chemotherapy (see footnote 1) (Buechner et al. 2017) (see Chap. 4).

2.2.3 Adults with Relapsed/Refractory B-ALL: Phase I Trial from Memorial Sloan Kettering Cancer Center (MSKCC)

Park et al. (2018) enrolled 83 adult (age range, 23–74 years) patients with relapsed B-cell ALL, of whom 53 who received an infusion of anti-CD19 autologous T cells costimulated with CD28. A total of 78 patients underwent leukapheresis, 11 of

[1] https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf. Accessed July 4, 2018.

whom did not undergo an attempt at cell production (owing to death or the receipt of alternative treatment), and 13 did not have cells infused (2 because of production failure and 11 owing to infection, alternative treatment, or death). A total of 36 patients (68%) received CAR T-cell therapy as a third or later salvage treatment, 12 (23%) had primary refractory disease, 19 (36%) had undergone allogeneic hematopoietic cell transplantation (allo-HCT) previously, and 13 (25%) had received blinatumomab previously. A total of 16 patients (30%) had Philadelphia chromosome-positive ALL, including 5 patients with the T315I ABL kinase mutation. Safety and long-term outcomes were assessed, as were their associations with demographic, clinical, and disease characteristics. After infusion, severe CRS occurred in 14 of 53 patients (26%; 95% confidence interval [CI], 15–40); 1 patient died. CR was observed in 83% of the patients. At a median follow-up of 29 months (range, 1–65), the median event-free survival (EFS) was 6.1 months (95% CI, 5.0–11.5), and the median overall survival (OS) was 12.9 months (95% CI, 8.7–23.4). Patients with a low disease burden (<5% bone marrow blasts) before treatment had markedly enhanced remission duration and survival, with a median EFS of 10.6 months (95% CI, 5.9 to not reached) and a median OS of 20.1 months (95% CI, 8.7 to not reached). Patients with a higher burden of disease (≥5% bone marrow blasts or extramedullary disease) had a greater incidence of the CRS and neurotoxic events and shorter long-term survival than did patients with a low disease burden (Gardner et al. 2017). The latter observation was also made by Maude et al. (2014) (see Chap. 5).

2.3 Non-Hodgkin B-Cell Lymphomas

2.3.1 Phase I, ZUMA-1 Study (Locke et al. 2017a): Primary Results of Axicabtagene Ciloleucel (KTE-C19) with a Focus on Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

In the phase I multicenter ZUMA-1 study, Locke et al. (2017a) evaluated KTE-C19, an autologous CD28-costimulated CAR T-cell therapy, in patients with refractory DLBCL. Patients received concurrent cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) for 3 days followed by KTE-C19 at a target dose of 2×10^6 CAR T cells/kg of recipient weight. The incidence of dose-limiting toxicity (DLT) was the primary endpoint. Seven patients were treated with KTE-C19, and one patient experienced a DLT of grade IV CRS and neurotoxicity. Grade ≥ III CRS and neurotoxicity were observed in 14% (n = 1 of 7) and 57% (n = 4 of 7) of patients, respectively. All other KTE-C19-related grade ≥III events resolved within 1 month. The overall response rate (ORR) was 71% (n = 5 of 7), and CR rate was 57% (n = 4 of 7). Three patients have ongoing CR (all at 12+ months) at the time of publication. CAR T cells demonstrated peak expansion within 2 weeks and continued to be detectable at 12+ months in patients with ongoing CR. Consistent with the *on-target, off-tumor* effect of KTE-C19, B-cell aplasia and hypogammaglobulinemia were observed in subjects with ongoing CR and persistent CAR T cells at 12 months

post-infusion. This multicenter study validated that centralized manufacturing is feasible and established the logistics for transportation of patient-specific product door to door within approximately 2 weeks (Locke et al. 2017a; Lulla and Ramos 2017) (see Chap. 6).

2.3.2 Additional Results of ZUMA-1 Study (Locke et al. 2017b) and US FDA Approval[2] (2017) of Axicabtagene Ciloleucel (KTE-C19)

The safety and efficacy of axicabtagene ciloleucel were established in a multicenter ZUMA-1 clinical trial of 101 adult patients with refractory or relapsed large B-cell lymphoma (Locke et al. 2017a, b). In the subsequent report data from patients enrolled into two cohorts consisting of DLBCL (cohort 1) and primary mediastinal B-cell lymphoma (PMBCL) or transformed follicular lymphoma (TFL) (cohort 2) were reported (Locke et al. 2017b). All patients had chemorefractory disease, with roughly 80% refractory to their last line of chemotherapy, and the remainder relapsing within 12 months of autologous hematopoietic cell transplant (auto-HCT). Patients had received a median of three prior therapies. Prior to infusion of axicabtagene ciloleucel, a conditioning regimen of Flu/Cy was administered. Axicabtagene ciloleucel was administered as a single infusion of modified autologous T cells at a target dose of 2×10^6 CAR^+ T cells/kg of recipient weight. The median follow-up for the primary analysis was 8.7 months, with most patients having data available for 6 months. There were four patients who experienced a CR but did not have assessment data available for 6 months. For the primary analysis, these individuals were classified as nonresponders, suggesting the response rates could be higher. The primary endpoint of the phase II study was ORR, which was significantly satisfied across the full study ($P < 0.0001$). After 6 months, 41% of patients were still in response, with a CR rate of 36% and a partial response (PR) rate of 5%. There was one incidence of a PR improving to a CR after 9 months, suggesting longer follow-up could further alter these numbers. Across the full duration of the study, those with DLBCL ($n = 77$) had an ORR of 82% and a CR rate of 49%. In the PMBCL/TFL group ($n = 24$), the ORR was 83% and the CR rate was 71%. After 6 months of follow-up, the ORR in the DLBCL group was 36%, which included a CR rate of 31%. In the PMBCL/TFL group, the 6-month ORR rate was 54%, with a CR rate of 50%. Median OS was not yet reached. The most common grade $\geq$ III AEs were anemia (43%), neutropenia (39%), decreased neutrophil count (32%), febrile neutropenia (31%), decreased white blood cell count (29%), thrombocytopenia (24%), encephalopathy (21%), and decreased lymphocyte count (20%). There were three fatal events in the study, two of which were deemed related to axicabtagene ciloleucel: hemophagocytic lymphohistiocytosis (HLH) and cardiac arrest in the setting of CRS. The third death was from pulmonary embolism. Data from 93 patients were available for

[2] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm. Accessed July 4, 2018.

the interim analysis from the ZUMA-1 trial (Locke et al. 2017a), whereas the primary assessment contained data for 101 patients (Locke et al. 2017b). With more patients assessed, the rate of CRS declined from 18% at the interim assessment to 13% for the primary analysis. Additionally, neurologic events dropped from 34% in the interim analysis to 28% in the primary assessment. There were no cases of cerebral edema. On the basis of these results, US FDA approved axicabtagene ciloleucel, for use in adult patients with certain types of large B-cell lymphoma after at least two other kinds of treatment have failed, including DLBCL, PMBCL, and DLBCL arising from TFL (see footnote 2). Notably, patients with primary central nervous system lymphoma were excluded from receiving axicabtagene ciloleucel, and the drug is not approved for treatment of patients with this condition.

2.3.3 Phase II Results of ZUMA-1 Study (Neelapu et al. 2017): Axicabtagene Ciloleucel in DLBCL, PMBCL, and Transformed FL

In a multicenter, phase II study, Neelapu et al. (2017) enrolled 111 patients with DLBCL, PMBCL, and TFL who had refractory disease despite undergoing recommended prior therapy. Patients received a target dose of 2×10^6 anti-CD19 CAR T cells/kg of recipient body weight after receiving a conditioning regimen of low-dose Flu/Cy. The primary end point was the rate of objective response (calculated as the combined rates of CR and PR). Secondary end points included OS, safety, and biomarker assessments. Among the 111 patients who were enrolled, axicabtagene ciloleucel was successfully manufactured for 110 (99%) and administered to 101 (91%) patients. The objective response rate was 82%, and the CR rate was 54%. These findings compare favorably with the results of the recent SCHOLAR-1 study (Crump et al. 2017) of conventional therapies for this disease, which showed an objective response rate of 26% and a complete response rate of 7%. With a median follow-up of 15.4 months, 42% of the patients were still in response, with 40% continuing to have a complete response. The overall rate of survival at 18 months was 52%. The most common AEs of grade III or higher during treatment were neutropenia (in 78% of the patients), anemia (in 43%), and thrombocytopenia (in 38%). Grade III or higher CRS and neurologic events occurred in 13% and 28% of the patients, respectively. Three of the patients died during treatment. In this particular study, higher CAR T-cell levels in blood were associated with response. Furthermore, this study (Neelapu et al. 2017) confirmed the feasibility and reliability of centralized manufacturing and coordination of leukapheresis procedures and shipping from multiple centers across the country. The product was manufactured for 99% of the enrolled patients and was administered to 91%. The short 17-day median turnaround time may be important for these patients with refractory large B-cell lymphoma, who generally have rapidly growing disease. The investigators of this multicenter trial (Neelapu et al. 2017) also reported that axicabtagene ciloleucel could be administered safely at medical facilities that perform transplantation, even if such centers had no specific experience in CAR T-cell therapy.