UPDATED RESULTS FROM THE CARTITUDE-1 STUDY OF CILTACABTAGENE AUTOLEUCEL, A B-CELL MATURATION ANTIGEN–DIRECTED CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Objectives: CARTITUDE-1 (NCT03548207) is a phase 1b/2 study of ciltacabtagene autoleucel (cilta-cel; JNJ-68284528), a chimeric antigen receptor T cell (CAR-T) therapy with two B-cell maturation antigen (BCMA)–targeting single-domain antibodies, in relapsed/refractory multiple myeloma (RRMM). Updated results from a median 18-month follow-up are reported here. **Material and methods:** Eligible patients had MM, received ≥3 prior regimens or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and had received a PI, IMiD, and anti-CD38 antibody. After apheresis, bridging therapy was allowed. Patients received a single cilta-cel infusion (target dose: 0.75×10^6 CAR + viable T cells/kg; range $0.5\text{-}1.0\times10^6$) 5–7 days (d) after lymphodepletion (300 mg/m^2 cyclophosphamide, 30 mg/m^2 fludarabine daily for 3 d). Primary objectives were to characterize cilta-cel safety, confirm the recommended phase 2 dose (phase 1b), and evaluate efficacy (phase 2). Cytokine release syndrome (CRS) was graded by Lee *et al* (Blood 2014) and neurotoxicity by CTCAE, v5.0 in phase 1b. CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded by American Society for Transplantation and Cellular Therapy (ASTCT) criteria in phase 2. Lee et al and CTCAE v5.0 were mapped to ASTCT for CRS and ICANS, respectively. **Results:** As of February 11, 2021, 97 patients (median of 6 prior lines) received cilta-cel. Overall response rate per independent review committee (primary endpoint) was 97.9% (95% CI, 92.7–99.7); 80.4% achieved stringent complete response (sCR) and 94.8% achieved very good partial response or better. Median time to first response was 1 month (mo) (range, 0.9–10.7), and median time to ≥CR was 2.6 mo (range, 0.9–15.2). Median duration of response was 21.8 mo (95% CI, 21.8–NE). Of 61 minimal residual disease (MRD)-evaluable patients, 91.8% were MRD negative at 10^{-5}. The 18-month progression-free survival (PFS) and overall survival rates (95% CI) were 66% (54.9–75.0) and 80.9% (71.4–87.6), respectively; median PFS was 22.8 mo (95% CI, 22.8–NE) for all patients, and not reached for patients with sCR. Grade 3/4 hematologic AEs ≥20% included neutropenia (95%), anemia (68%), leukopenia (61%), thrombocytopenia (60%), and lymphopenia (50%). CRS occurred in 95% of patients (4% grade 3/4); median time to onset was 7 d (range, 1–12) and median duration was 4 d (range, 1–14, excluding 1 patient with 97-d duration). CRS resolved in all but one with grade 5 CRS/hemophagocytic lymphohistiocytosis. 21% of patients had CAR-T neurotoxicity (grade ≥3, 10%). Twenty-one deaths occurred during the study: none ≤30 days; 2 ≤100 days; and 19 >100 days after infusion, among which, 10 were due to disease progression, 6 were treatment-related as assessed by the investigator, and 5 were due to AEs unrelated to treatment. **Discussion:** Cilta-cel is under further investigation in other MM populations in earlier lines of therapy and in outpatient settings. **Conclusions:** At a longer median follow-up of 18 mo, a single cilta-cel infusion yielded early, deep, and durable responses with a manageable safety, in heavily pretreated patients with MM.

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USING A NONVIRAL AND NONINTEGRATING DNA VECTOR TO GENERATE SAFE CAR-T CELLS

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Aims: CAR-T cell therapy has proven its importance in cancer treatment and currently there are five approved products on the market. However, these products are based on viral vectors, which presents a risk of insertional mutagenesis, it can also be immunogenic and its manufacture is extremely expensive. The development of a nonviral vector, suitable for

an efficient and stable transfection of NK and T cells is the goal of this study. **Methods:** In this study we use a special episomal vector (extrachromosomal vectors) with i) scaffold/matrix attachment region (S/MAR) motifs that can actively mediate the episomal maintenance, ii) a plasmid replication enhancer, the replication-Initiation Region (IR) from the β-globin locus (pEP-IR) and iii) a CAR anti CD19 (pEP-IR-CAR). We electroporated activated and non-activated T cells and NK cells with different plasmid concentrations. We evaluated transfection efficiency and viability. **Results and discussion:** Our findings showed that unstimulated T cells are transfected more efficiently than activated T cells. Transfection of unstimulated T cells with 20 ug of supercoiled pEP-IR-GFP plasmid reached 22 to 63% of GFP and viability around 54% depending on the culture condition used after electroporation (FBS% and IL2). We then accessed the efficacy of pEP-IR-CAR and CAR expression, confirmed in 3,2% of the cells with 89% of viability. Cells expressing CAR on their surface were marked with anti-CAR antibody Biotin-SP-conjugated and selected by anti-Biotin microbeads, achieving an enrichment of 54,9% CAR+ cells. **Conclusions:** Our results showed that we established an optimized protocol resulting in an acceptable transfection efficiency and the transfected cells can be selected. So, the next step is to perform *in vitro* cytotoxicity and *in vivo* assays with the episomal CAR+ cells. **Funding:** Financially supported by FAPESP 2020/09206-4, FAPESP 2019/25309-0, CTC Center for Cell-based Therapy (FAPESP 2013/08135-2), and National Institute of Science and Technology in Stem Cell and Cell Therapy (CNPq 573754-2008-0 and FAPESP 2008/578773).

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HEMATOLOGIA PEDIÁTRICA

ACIDENTE VASCULAR CEREBRAL COMO COMPLICAÇÃO EM DOENÇA FALCIFORME SC

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Introdução: A Doença Falciforme (SS) é considerada de maior risco para vasculopatias crônicas em SNC culminando, geralmente, com eventos de acidente vascular cerebral isquêmico (AVCI). Ocorrem lesões das grandes artérias do círculo de Willis, por hiperplasia da camada íntima e proliferação muscular e de fibroblastos, culminando na formação de estreitamentos segmentares na luz de grandes e médias artérias. Aos 20 anos de idade, 11% e, aos 45 anos, 24% dos pacientes já tiveram AVCI. A maior incidência ocorre nas crianças entre 2 a 9 anos, voltando a aumentar após os 20 anos, sendo a média das idades em 13,8 anos. O risco de isquemia cerebral (sintomática ou silenciosa) no decorrer da vida do paciente é de 30%. Pacientes com dupla heterozigose das hemoglobinas S e C – DF(SC) seguem curso clínico mais brando, sendo muito raro eventos macrovasculares. **Relato de caso:** Sexo masculino, 18 anos, com DF(SC), com várias internações prévias, cerca de 3-5/ano dos 6 aos 10 anos de idade, posteriormente com uma internação ao ano, por crises dolorosas. Aos 8 anos, submetido à colecistectomia. Aos 13 anos, relatou a presença de diminuição discreta da movimentação do membro superior esquerdo (MSE) observado há 3 meses, com piora progressiva da força muscular, relatando dificuldade para pegar objetos, tremores na mão esquerda ao levantar peso, dificuldade para abrir e fechar a mão e estender o membro. Ao exame neurológico: hemiparesia à esquerda desproporcionada, força grau IV em todos os membros, porém diminuída em região distal de MSE (grau III). Rigidez articular distal, rotação incompleta do ombro esquerdo, tônus adequado, discreta hipotrofia de musculatura interfalangeana à esquerda . Marcha atípica com hiperreflexia em MSE e hipertonia em hemicorpo esquerdo. AngioRM crânio: Alteração de sinal no centro semioval direito associada à discreta atrofia que deve corresponder à área sequelar por evento isquêmico, com comprometimento focal das fibras do trato corticospinal. Introduzido hidroxiuréia, sem aumento de HbF e elevação dos valores de Hb, sendo suspenso. Iniciado transfusões de troca mensais, porém não foi possível atingir o alvo de HbS < 30%. Como apresenta hemoglobina basal de 13–14g/dL, optado por manter apenas esquema de sangrias mensais com o objetivo de reduzir viscosidade sanguínea. **Discussão:** A dupla heterozigose com HbS e HbC – DF(SC) determina uma doença mais branda: quadro hemolítico menos intenso, eventos agudos microvasculares menos intensos e macrovasculares (principalmente em SNC), bastante raros. Alguns estudos relataram que velocidades de fluxo sanguíneo ao doppler TC > 128 cm/s são anormalmente elevadas para pacientes SC e devem ser monitorados. A terapia com hidroxiuréia mostrou-se benéfica em alguns casos, diminuindo a taxa de eventos vaso-oclusivos. O aumento de hemoglobina pode levar a síndrome de hiperviscosidade, sendo indicada neste caso a flebotomia terapêutica. **Comentários:** Pacientes com Doença Falciforme (SC) podem apresentar as mesmas complicações que as formas mais severas, mas com frequência reduzida e, um pequeno subconjunto de indivíduos com DF(SC) tem fenótipo clínico semelhante ao SS. Futuros estudos são necessários para avaliar risco de AVCI em formas mais brandas da doença.

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ACIDENTE VASCULAR CEREBRAL ISQUÊMICO COMO COMPLICAÇÃO PRECOCE EM DOENÇA FALCIFORME

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Introdução: Os infartos cerebrais em indivíduos com doença falciforme (DF), em geral diferem da etiologia da população geral, pois devem-se a hemodinâmica cerebral alterada em função da hemólise crônica, baixas concentrações de hemoglobina (Hb), desrregulação vasomotora e estado pró-