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PNEUMONIA ORGANIZANTE CRIPTOGÊNICA EM PACIENTE COM LEUCEMIA PROMIELOCÍTICA AGUDA SUBMETIDA A TMO AUTÓLOGO: UM DESAFIO DIAGNÓSTICO E TERAPÊUTICO

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Introdução: A pneumonia organizante criptogênica (COP), anteriormente conhecida como BOOP (Bronchiolitis Obliterans Organizing Pneumonia), é uma forma incomum de doença pulmonar intersticial caracterizada por inflamação e organização do parênquima pulmonar. Embora geralmente idiopática, pode ser secundária a diversas condições, como infecções, medicamentos, radioterapia e neoplasias hematológicas. Em pacientes submetidos a transplante de células-tronco hematopoiéticas (TCTH), especialmente os com história recente de quimioterapia intensiva, a COP representa um diagnóstico desafiador, com apresentação clínica e radiológica inespecífica, muitas vezes mimetizando infecções ou progressão da doença de base. **Relato de caso:** Paciente feminina, 33 anos, previamente hígida, foi diagnosticada com leucemia promielocítica aguda (LPA) de alto risco em Setembro de 2023. Após falha terapêutica inicial, foi submetida ao tratamento com ATRA+ATO em segunda linha, completando seis ciclos com boa resposta. Em março de 2025, realizou TCTH autólogo com condicionamento BUCY (bussulfano + ciclofosfamida), sem intercorrências durante a internação. Teve pega plaquetária no D+10 e neutrofílica no D+11. Cerca de dois meses após o transplante, apresentou dor torácica e dispneia, procurando ambulatório de hematologia para avaliação e, após, foi encaminhada à emergência por dessaturação e taquicardia. A angiotomografia de tórax evidenciou consolidações e vidro fosco bilaterais, sem sinais de tromboembolismo pulmonar. Apresentava exames virais negativos e foram, então, iniciados antibióticos de amplo espectro e mantida vigilância respiratória em enfermaria. Apresentou progressiva piora ventilatória com necessidade de UTI, ventilação mecânica invasiva, escalonamento antimicrobiano com inclusive cobertura para agentes oportunistas (CMV, pneumocystis, aspergillus) e pulsoterapia com metilprednisolona pois não se podia afastar toxicidade por medicações previamente utilizadas. Paciente seguiu em piora clínica, e dias após admissão na UTI, ainda teve sorologia positiva para Influenza A. Realizou-se biópsia pulmonar a céu aberto, compatível com fibrose pulmonar, e, a imunohistoquímica da peça foi positiva para adenovírus. Vinha em uso de metilprednisolona 2 mg/kg/dia e micofenolato de mofetila 2g/dia, mas, apesar das medidas, paciente evoluiu com ventilação mecânica pesada prolongada, infecção por bactéria KPC-NDM, sendo considerada falência respiratória e priorizadas medidas de conforto, evoluindo a óbito poucos dias após. **Conclusão:** A COP é rara em pacientes com LPA tratados com TCTH autólogo, e seu diagnóstico é frequentemente retardado pela semelhança clínica e radiológica com pneumonias infecciosas, comuns nesse contexto. A biópsia pulmonar é essencial para melhor esclarecimento do quadro. A associação de lesão alveolar, imunossupressão, múltiplas exposições medicamentosas e infecções virais pode atuar como fator desencadeante da COP. O prognóstico é variável, e formas agressivas com fibrose extensa podem não responder adequadamente ao tratamento com corticoides e imunossupressores. Este caso ilustra a importância do reconhecimento precoce da COP como diagnóstico diferencial em pacientes hematológicos com insuficiência respiratória de causa indefinida.

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POSTTRANSPLANT CYCLOPHOSPHAMIDE OR ANTI-THYMOCYTE GLOBULIN FOR UNRELATED DONOR HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Posttransplant cyclophosphamide (PTCy) has been increasingly used in unrelated donor (URD) hematopoietic cell transplantation (HCT) based on two phase III trials that have compared PTCy with conventional prophylaxis. However, a robust comparison with anti-thymocyte globulin (ATG) is not available. **Aim:** Compare PTCy and ATG in patients undergoing URD HCT. **Material and methods:** This registry-based cohort study included patients who underwent hematopoietic cell transplantation in the United States from 2017 to 2021. Data were sourced from a Center for International Blood and Marrow Transplant Research (CIBMTR) registry database. We included patients diagnosed with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or myelodysplastic syndrome (MDS) who received HCT using matched or mismatched URD HCT with PTCy or ATG (those receiving both were excluded). The primary outcomes were relapse-free survival (RFS) and moderate to severe chronic GVHD (mod/sev cGVHD). Secondary outcomes included overall survival (OS), relapse (REL), non-relapse mortality (NRM), and grades II-IV and III-IV acute GVHD (aGVHD II-IV and aGVHD III-IV). Univariable analysis was performed with Kaplan-Meier and cumulative incidence curves and compared with the logrank and Gray tests, respectively. Multivariable analyses were performed using cause-specific Cox models controlling for patient age and sex, disease, conditioning regimen, graft source, donor age, HLA match, and year of transplant. All analyses were conducted with R, version 4.1.1, from the R Foundation for Statistical Computing, Vienna, Austria. **Results:** With a median follow-up of 36 months, 4,750 patients

were included (2,271 with PTCy and 2,479 with ATG). The median age was 61 years (range: 18-81), and 44% were female. AML was the most common diagnosis (54%), followed by MDS (30%) and ALL (16%). 45% received a myeloablative conditioning regimen, and peripheral blood was the preferred graft source (90%). Except for HLA matching (HLA 7/8 in 26% of the PTCy group and 9% in the ATG group) and the year of transplant (PTCy was more common in later years), all variables were well-balanced. 2y-RFS was 49% for PTCy and 43% for ATG ($p = 0.001$). 2y-mod/sev cGVHD was 12% for PTCy and 23% for ATG ($p < 0.001$). RFS improved with PTCy (HR = 0.83, 95%CI 0.76-0.91, $p<0.001$) as well as mod/sev cGVHD (HR = 0.45, 95%CI 0.38-0.53, $p < 0.001$), compared to ATG. OS also improved (HR = 0.77, 95%CI 0.70-0.85, $p < 0.001$), mainly because of lower NRM (HR = 0.66, 95%CI 0.58-0.76, $p < 0.001$). There was no effect on relapse (HR = 0.95, 95%CI 0.85-1.07, $p = 0.44$). Grades II-IV (HR = 0.60, 95%CI 0.54-0.67, $p < 0.001$) and III-IV aGVHD (HR = 0.44, 95%CI 0.36-0.55, $p < 0.001$) were also less common with PTCy compared to ATG. The same results held when (1) HLA 7/8 mismatched HCT were excluded or (2) when analyses were stratified by transplant year. **Discussion and conclusion:** Within this large and contemporary CIBTMR database, outcomes with PTCy-based GVHD prophylaxis were better than ATG in every studied aspect except relapse, leading to higher RFS and OS and improved GVHD control. Although registry-based, the groups were well-balanced, and the large patient cohort (nearly 5,000 individuals) enabled us to develop a Cox model that controlled for all possible confounding factors, minimizing bias. Our findings suggest that PTCy should be preferred over ATG in unrelated donor transplantation.

References: Shaffer et al, DOI: 10.1200/JCO.24.00184

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POSTTRANSPLANT CYCLOPHOSPHAMIDE-BASED HAPLOIDENTICAL TRANSPLANTATION, WITH MMF 30 MG/KG, COMPARED WITH UNRELATED DONOR TRANSPLANTATION WITH ATG 6 MG/KG, WITH BONE MARROW OR PERIPHERAL BLOOD STEM CELL GRAFTS

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Introduction: Several adaptations have been reported since the introduction of posttransplant cyclophosphamide (PTCy)-based haploidentical (Haplo) hematopoietic cell transplantation (HCT) using a non-myeloablative platform and a bone marrow (BM) graft source. Reduced doses of mycophenolate mofetil (MMF) have been successfully tested, as well as combinations with earlier administration of immunosuppression, postponing the second PTCy dose to D+5, and using peripheral blood grafts (PBSC). **Aim:** This study aims to compare the outcomes of PTCy-based haploidentical transplantation with MMF at 30 mg/kg to a concurrent cohort of unrelated donors (URD) who received ATG-based GVHD prophylaxis at 6 mg/kg prior to transplantation, using either BM or PBSC grafts. **Material and methods:** This single-center observational study included patients with hematological malignancies who underwent Haplo or URD HCT between November 16, 2016, and December 31, 2024. Univariable analyses were performed using Kaplan-Meier and cumulative incidence methods. Multivariable analyses were conducted with Cox models, with the URD-BM group serving as the reference category unless otherwise specified. The local ethics committee approved this study, which was registered at ClinicalTrials.gov under NCT02759822. **Results:** We included 174 patients, with a median follow-up of 32 months. Patients receiving BM were younger (median age: 15 vs. 34 years), and they were more likely to receive a myeloablative (MAC) regimen (92% vs. 75%, compared to PBSC); the frequency of a MAC regimen was also higher with URD (94% vs. 74%, compared with Haplo). 18% of the URD were HLA 7/8 mismatched, while the others were 8/8 matched. Other patient characteristics were well-balanced. Two-year overall survival (OS) for Haplo-PBSC was 47%, which was not significantly lower than that for URD-BM (70%), URD-PBSC (61%), and Haplo-BM (64%, $p = 0.18$). In multivariable analysis, Haplo-PBSC was linked to a higher risk of death (HR = 2.28, $p = 0.03$) compared to URD-BM, mainly due to higher non-relapse mortality (HR = 2.67, $p = 0.02$). The relapse rate was similar across the groups. PBSC grafts, whether with URD (HR = 1.95, $p = 0.04$) or Haplo (HR = 3.13, $p < 0.01$) donor, significantly increased grades II-IV aGVHD, while only the latter was non-significantly associated with grades III-IV aGVHD (HR = 2.39, $p = 0.09$). The only protective factor against cGVHD, across all grades and moderate to severe cases, was the combination of URD and BM (HR = 0.54, $p = 0.03$; and HR = 0.43, $p = 0.02$, respectively), compared with Haplo with BM or PBSC or URD with PBSC. **Discussion and conclusion:** Our results show that OS is lower with a Haplo-PBSC transplant compared to a URD or Haplo-BM transplant due to higher non-relapse mortality. PBSC increases all severe forms of aGVHD, and the rate of moderate or severe cGVHD is higher with Haplo with BM or PBSC or URD with PBSC, compared to URD with BM. More effective cGVHD prophylaxis for PBSC grafts is needed. In summary, we have demonstrated that MMF 30 mg/kg may reduce survival when combined with Haplo-PBSC. However, it seems to be safe for Haplo-BM despite higher rates of cGVHD compared with URD-BM.

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PREVALÊNCIA DAS MUTAÇÕES QUE POSSAM CONFERIR RESISTÊNCIA AOS MEDICAMENTOS UTILIZADOS NO TRATAMENTO DO CITOMEGALOVÍRUS

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