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IMMUNE PROFILING EVALUATION OF NEWLY DIAGNOSE MULTIPLE MYELOMA (NDMM) TRANSPLANT ELIGIBLE (TE) PATIENTS TREATED WITH DARATUMUMAB, CYCLOPHOSPHAMIDE, THALIDOMIDE AND DEXAMETHASONE (DARA-CTD): PRELIMINARY RESULTS

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Objective: Primary endpoint was to quantify lymphocytes subpopulations in (NDMM) (TE) patients at different treatment phases. Secondary endpoint was to evaluate B cells subsets at same times. **Methods:** Peripheral blood of 10 NDMM TE patients was collected at three different moments: at diagnose, after 4 induction cycles and after two consolidation cycles post- (ASCT). Dara-CTd protocol was for up to four 28-day induction cycles: C-500 mg per oral (PO) d 1,8 and 15, T at 100-200 mg PO d 1 to 28, Dex at 40 mg PO d 1,8,15 and 22 and Dara 16 mg/kg/dose IV on d 1,8,15 and 22 during cycles 1 - 2 and every other week in cycles 3 – 4, followed by ASCT. Consolidation was started at D+30 after ASCT and all patients received up to four 28-day consolidation cycles: Dara 16 mg/kg and (D) at 40 mg every other week, associated with T at 100 mg PO d 1 - 28. Dara 16 mg/kg was used monthly as maintenance until progression or limiting toxicity. Flow cytometry was used to detect lymphocyte surface by CD3, CD4, CD5, CD8, CD16, CD19, CD20, CD38, CD45 and CD56 in the scatter plot. B cells were isolated and subpopulations (naïve B cells, class and non-class switched memory B cells, IgD-CD27- memory B cells and plasmablasts) were detected by CD20, CD24, CD27, CD38, CD45 and IgD. Statistical analysis was performed using the SPSS® v25.0. **Results:** The median number of lymphocytes subsets at diagnosis was 1.139 x 10^3/μL for T cells, 155 x 10^3/μL for B cells and 284 x 10^3/μL for NK cells. After four cycles of Dara-CTD the median number of T, B and NK cells had dropped to 834, 7.5 and 8.0 x 10^3/μL respectively ($p \leq 0.05$). After two consolidation cycles post-ASCT, the T cells showed full reconstitution (1.246 x 10^3/μL) while B cells and NK cells had weakly reconstitution (20 x 10^3/μL and 33 x 10^3/μL, respectively). Regarding B cells subpopulations, the median B cell naïve numbers decreased from 32 x 10^3/μL to 1 x 10^3/μL (after 4 cycles), and recovery post-ASCT to 14 x 10^3/μL. Class and non-class switched memory B cells numbers decreased after induction from 30 to 3.5 x 10^3/μL and 37 to 2.0 x 10^3/μL respectively. These subpopulations recovery after ASCT+ two consolidation cycles were not observed. **Discussion:** Different cells expresses CD38 antigen in their surface and depending on that, lymphocytes counts reduction have been shown with different protocols using Dara. The present study confirmed that there is a decrease on total lymphocytes numbers after Dara- use. After two consolidation cycles post-ASCT, T cells counts had been recovered, while NK and B cells had a slightly recovery suggesting that Dara-CTD combination had a slighted negative impact in those lymphocytes'reconstitution. Concerning specially B cells populations, we found that naive B cell was the first to showed recovery, although it was still below the reference range (33 – 259 x 10^3/μL). **Conclusion:** This is the first study that reported lymphocyte profile with Dara plus CTD protocol. The preliminary data suggests that Dara-CTD reduces all lymphocytes populations after induction phase, but after ASCT followed by two consolidations cycles full reconstitution of T cells and slight recovery of B and NK cells was observed.

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IMPLICAÇÕES DA VIA DE SINALIZAÇÃO REDOX DE CÉLULAS TRONCO NO PERFIL DE SOBREVIVÊNCIA DE PACIENTES PORTADORES DE MIELOMA MÚLTIPLO

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Objetivos: A partir do estudo do transcriptoma de células-tronco de pacientes portadores de Mieloma Múltiplo (MM), tivemos o objetivo de validar o perfil da via de sinalização redox e de estresse oxidativo entre vivos e óbitos. **Material e métodos:** As amostras foram obtidas após assinatura do termo de consentimento livre e esclarecido e divididas em 2 grupos de comparação: pacientes vivos versus óbitos (óbito até 6 meses pós TMO). Para o transcriptoma, foi analisado o produto de leucoaférese de 28 pacientes com MM elegíveis para transplante autólogo de medula óssea (MO),

mobilizados com fator estimulador de colônia de granulocitos (G-CSF). O RNA foi obtido utilizando-se o *RNeasy Mini Kit* (Qiagen, CA, EUA) e o transcriptoma analisado pelo sistema *GeneChip Exon Humano 1,0 ST Array* (Affymetrix, CA, EUA). Analisados com o *software Partek®* (http://www.partek.com) e pelo programa Metacore/portal Genego (Thomson Reuters), elencando vias superexpressas maior ou igual a 2 vezes (*Up regulation ou down regulation*). Foi selecionada para validação a via de sinalização redox e estresse oxidativo, analisando o produto de leucoaférese de 11 pacientes nas mesmas condições acima citadas. O perfil redox foi obtido através da avaliação de níveis circulantes de hidroperóxidos induzido por Butil (QL) e o perfil antioxidante medido através da capacidade antioxidante total (TRAP), ambos pela técnica de quimioluminescência de alta sensibilidade em tempo real. Foi calculado o índice de estresse através da relação pró/antioxidante. Os dados foram analisados no *software OriginLab* 9.0 e as comparações feitas no *software GrapPadPrism* 7.0 ($p \leq 0,05$). **Resultados:** No perfil global não foram observadas diferenças significantes em relação à comparação dos perfis pró e antioxidante dos pacientes vivos versus óbitos, sendo a média de QL (2094539,429 e 2173588,75), do TRAP (1,409 e 1,281) e índice de estresse (1672569,885 e 2016150,010), óbitos e vivos respectivamente. No transcriptoma, as principais vias associadas aos genes diferencialmente expressos foram inflamação e resposta imune, estresse oxidativo e neuroimunomodulação. No grupo óbito observou-se que a capacidade antioxidante de células tronco de pacientes portadores de plasmocitoma foi 50% menor que no grupo sem plasmocitoma. Não foram observadas diferenças no perfil de estresse em relação ao padrão de resposta ao tratamento (parcial x completa). **Discussão:** é bem documentado que mudanças no balanço redox de células tronco podem causar o estresse oxidativo. O balanço redox é potencializador de quimiorresistência pela alteração na indução de apoptose, sendo alterado por algumas substancias. Um exemplo controverso é a glutationa (GSH) que age como antioxidante mas sem papel definido no prognostico final do paciente com MM. Já na presença do plasmocitoma, sabemos que ele se expande mediado por citocinas secretadas por plasmócitos malignos, e pode estar relacionada com o aumento do estresse oxidativo versus óbito. **Conclusão:** Até onde sabemos, este é o primeiro estudo com foco em análise do perfil redox de células tronco de pacientes com MO. Os achados permitem concluir que existem variações no perfil de estresse oxidativo das células tronco em relação à presença de plasmocitoma no grupo óbito, sem variações para os demais perfis analisados e sem diferença nas comparações entre vivos e óbitos, sugerindo que o estresse oxidativo pode estar implicado neste modelo em situações específicas.

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ISATUXIMAB PLUS CARFILZOMIB AND DEXAMETHASONE VS CARFILZOMIB AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (IKEMA): INTERIM ANALYSIS OF A PHASE 3, RANDOMIZED, OPEN-LABEL STUDY

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Objective: To demonstrate benefit of adding Isatuximab (Isa) to (Kd) vs Kd in relapsed/refractory multiple myeloma (RRMM). **Methods:** In this Phase-3 study (NCT03275285), patients with RRMM and 1-3 prior lines of therapy were randomized 3:2 and stratified by number of prior lines and R-ISS to receive Isa-Kd or Kd. Isa-Kd arm received Isa (10 mg/kg IV) weekly for 4 weeks, then every 2 weeks. Both arms received K (20 mg/m^2 days 1-2, 56 mg/m^2 thereafter) twice-weekly for 3 of 4 weeks, and d (20 mg) twice-weekly. Treatment continued until disease progression or unacceptable adverse events (AE). Primary objective: increase in PFS of Isa-Kd vs Kd, determined by an Independent Response Committee (IRC). Comparison between arms conducted through log-rank testing. Key secondary objectives: overall response rate (ORR), rate of very good partial response (VGPR) or better, complete response (CR) rate, MRD negativity-rate (105 by NGS), and overall survival (OS). Key secondary endpoints tested with a closed test procedure. Safety data included treatment emergent adverse events (TEAE), hematological, and biochemistry results for all patients. Interim efficacy analysis was planned once 65% of total expected PFS events were observed. **Results:** 302 patients (Isa-Kd: 179, Kd: 123) were randomized. Median age 64 (33-90) years; R-ISS I, II, III was 25.8%, 59.6%, 7.9% respectively; 44%, 33% and 23% had 1, 2 and ≥3 prior lines respectively; 90% and 78% had prior proteasome inhibitor and IMiD respectively; 24% had high-risk cytogenetics. At a median follow-up