Poster P.11.93

HEMATOPOIETIC STEM CELL GENE THERAPY FOR MUCOPOLYSACCHARIDOSIS TYPE I, HURLER VARIANT (MPS-IH).

Bernardo M.E.*[1], Gentner B.[1], Tucci F.[1], Fumagalli F.[1], Ciotti F.[1], Sarzana M.[1], Pontesilli S.[2], Baldoli C.[2], Filisetti C.[2], Miglietta S.[1], Acquati S.[1], Redaelli D.[1], Zonari E.[1], Rovelli A.[3], Parini R.[3], La Marca G.[4], Naldini L.[1], Aiuti A.[1]

[1]SR-Tiget ~ Milano ~ Italy, [2]Ospedale San Raffaele ~ Milano ~ Italy, [3]Ospedale San Gerardo ~ Monza ~ Italy, [4]Ospedale Meyer ~ Firenze ~ Italy

Introduction
Mucopolysaccharidosis type I Hurler (MPSIH) is a lysosomal storage disease due to α-L-iduronidase (IDUA) deficiency. The current therapeutic strategy is allogeneic hematopoietic stem cell (HSC) transplantation which shows limited efficacy on bone and neurocognitive development.
Methods
A Phase I/II HSC-gene therapy (GT) trial opened in May 2018 evaluating safety, tolerability and efficacy of autologous, IDUA lentiviral-transduced CD34+ cells in MPSIH patients (pt) undergoing myeloablative conditioning. The study foresees the enrollment of 6 pt who lack a non-heterozygous HLA-matched donor and display an IQ/DQ>70. Primary endpoint of efficacy is IDUA activity in peripheral blood up to supraphysiologic levels at 1 year post-GT. Treatment impact on nervous system and bone is assessed by measurement of IDUA in CSF, DQ/IQ and specific radiologic parameters.
Results
By July 2019, six patients have been treated at a median age of 24 months (range: 14-34), with a median follow up of 4 months (range: 1-13). HSC harvest by mobilization was uneventful and effective resulting in cryopreserved drug products of resulting in drug products with a median of 21 million CD34+cells/kg (range: 13-29); in evaluable pt hematologic recovery was fast. Pt 1 and 2 reached supra-normal levels of IDUA activity by day+14 and stabilized at 10 folds above the mean of normal range, along with an in vivo vector copy number ranging from 2 to 4 in multiple hematopoietic lineages. Early after GT (d+90) IDUA activity was detected in CSF, and urinary GAGs were reduced to near-normal levels. Pt 1 maintained these results at d+180. From 2 months after GT his growth velocity (cm/y) shifted from -2.4 to 0.5 SD. Other pt are currently under evaluation.
Conclusion
Our preliminary results suggest an early metabolic correction of the enzyme defect. Long term-follow up and treatment of further pt are needed to confirm that IDUA supranormal levels result in improvement of neurological and bone outcomes as compared with allogeneic HSC transplantation.

Terapia genica ex-vivo con cellule staminali ematopoietiche per la Mucopolisaccaridosi di tipo I, Hurler

Fraldi A, Serafini M, Sorrentino NC, Gentner B, Aiuti A, Bernardo ME. Gene therapy for mucopolysaccharidoses: in vivo and ex vivo approaches. Ital J Pediatr. 2018 Nov 16;44(Suppl 2):130. doi: 10.1186/s13052-018-0565-y.

Mucopolisaccaridosi di tipo I Hurler

Coordinator: Alessandro Aiuti
Partners: Maria Ester Bernardo; Bernard Gentner

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