COMBINED ENZYME REPLACEMENT THERAPY AND HEMOPOIETIC STEM CELL TRANSPLANTATION IN MUCOPOLYSACCHARIDOSIS

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What is enzyme replacement therapy (ERT)?

- A medical treatment replacing an enzyme in patients in whom that particular enzyme is deficient or absent.
- ERT is currently available for some lysosomal storage disorders
- ERT is usually given by regular intravenous infusions

What is Hemopoietic Stem Cell Transplantation (HSCT) ?

- A medical treatment that involves the transplantation of stem cells derived from bone marrow or blood.
- Peripheral blood is now the most common source of stem cells.
- Stem cells are cells that have the ability to renew themselves through cell division and differentiate into a diverse range of specialized cell types.

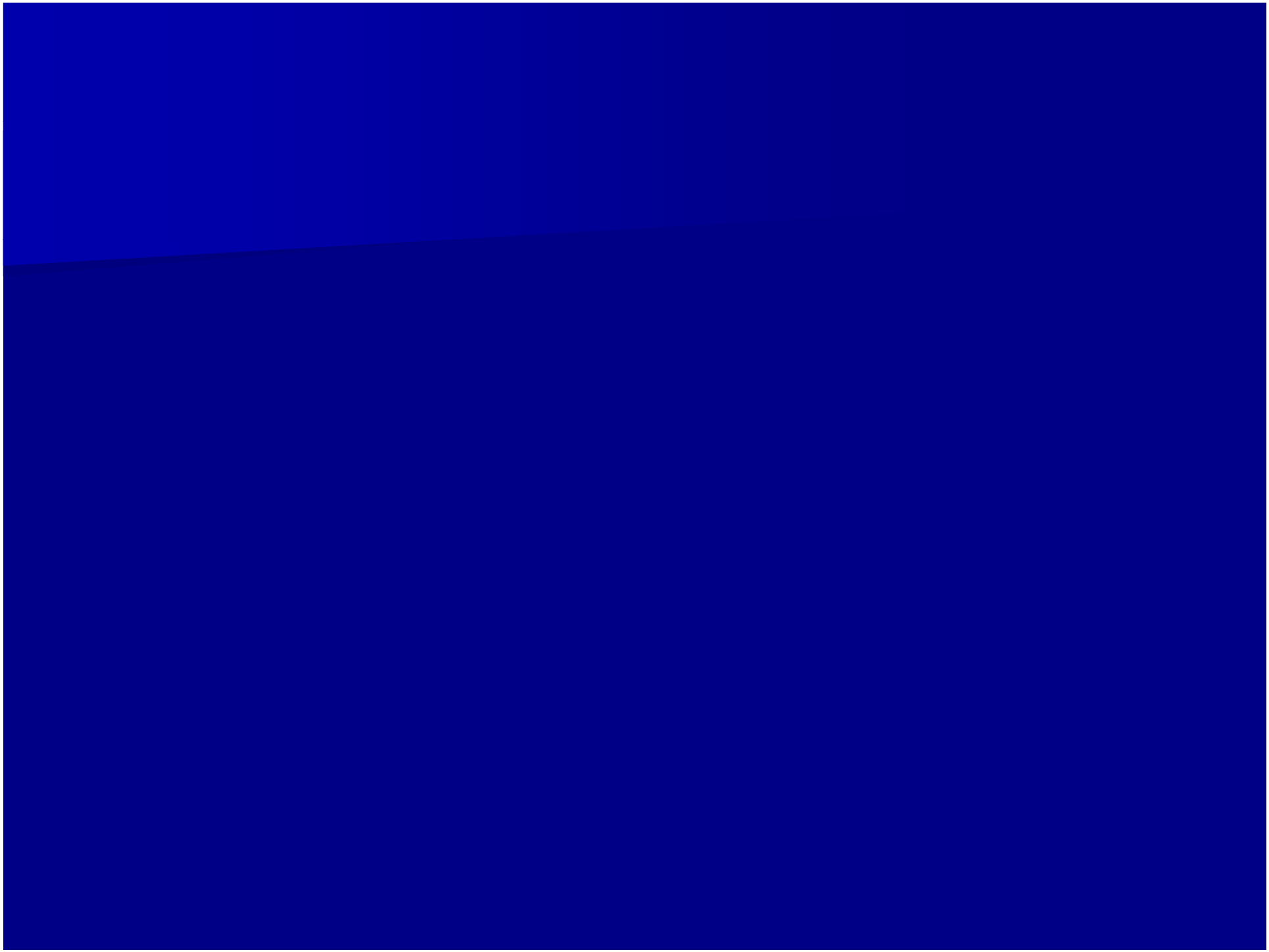
Hemopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation remains a risky procedure with many possible early and late complications.

In general in recent years, survival rates have gradually improved across almost all patient populations receiving transplants.

What is combined ERT/ HSCT ?

- A treatment period with ERT
- HSCT
- Ongoing ERT during and post transplantation



Case report

13 month old girl presented with recurrent upper respiratory tract infections, mild developmental delay, coarse facial features, hepatosplenomegaly.

- elevated urinary glycosaminoglycans
- reduced level α – L- iduronidase,
  - 5.0pmol/min/mg protein (normal range 15 – 134pmol/min/mg protein).
- Homozygous p.Q70X mutation *IDU* gene.
- Patient diagnosed with MPS I, Hurler syndrome

At diagnosis

mild developmentally delayed
coarse facial features
poor growth
corneal opacification
umbilical hernia, hepatosplenomegaly,
restricted joint movement
lumbar kyphosis

Sleep study: significant upper airway obstruction with severe obstructive sleep apnoea requiring CPAP.

Echocardiogram: dysplastic and prolapsing incompetent mitral valve, dilated cardiomyopathy and moderately severe left ventricular dysfunction

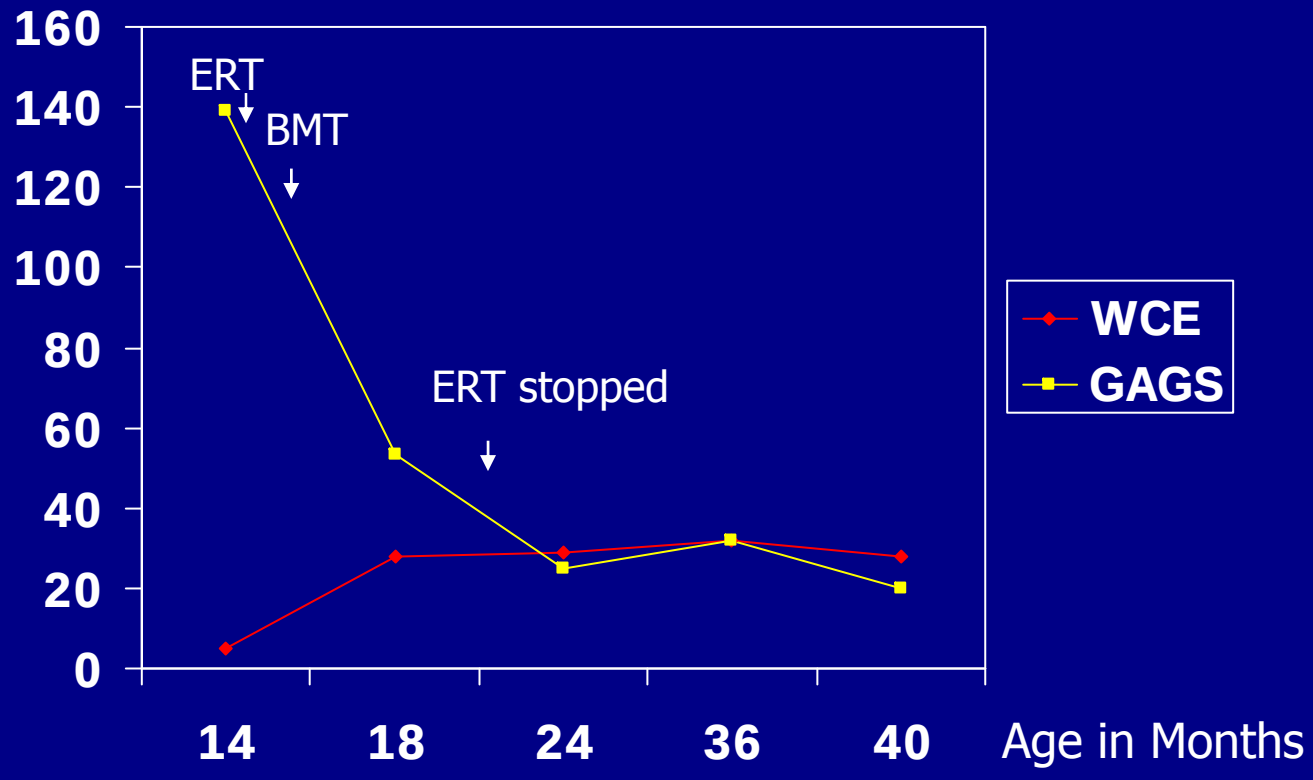
Treatment

- Weekly infusion of Aldurazyme®, 0.58mg/kg (100U/kg) for 8 weeks
- Matched sibling donor identified
- Modified conditioning regimen
- BMT
- ERT continued for 12 weeks post BMT and there was evidence of donor cell engraftment.

Outcome

- Combined ERT/BMT treatment was well tolerated.
- No signs of graft versus host disease.
- Resolution of obstructive sleep apnoea and hepatosplenomegaly.
- Improvement in cardiac function

α – L- iduronidase activity & urinary GAGS



Outcome at 40 months (2 years post BMT)

- Improvement in growth,
  - Height increased 2nd percentile → 20th percentile,
    Weight maintained 5th percentile,
    Head circumference 25th percentile
- Small umbilical hernia
- Residual corneal clouding
- Improved cardiac function
- Improved joint range of movement
- Improved hearing
- Developmental progress, but shows mild delays across all developmental domains.
  Developmental age equivalence - 31months

Things which have not improved

- Finger contractures
- Kyphosis lumbar spine
- Coxa valga and mild subluxation of both femoral heads

Patient at 40 months

Sibling BMT donor

Combined ERT / HSCT for MPS I

Until recently HSCT was regarded as the treatment of choice for children less than 2 years with MPS I who had minimal or no central nervous system disease.

However HSCT alone is associated with a high transplant morbidity and mortality

ERT prior to and following HSCT corrects the enzyme deficiency until endogenous enzyme production is established, reverses airway obstruction and cardiovascular complications thus reducing morbidity and mortality at the time of transplant.

Recent case series of combined ERT & HSCT in MPS I Hurler compared with HSCT alone

Study	Number of patients	Conditioning regimen	ERT pre & post	Survival (first transplantation attempt)	Alive and engrafted (first transplantation attempt)
Grewal et al (2005)	12	Varied	Yes	92%	67%
Cox-Brinkman et al (2006)	22	Varied	Yes	91%	59%
Tolar et al (2008)	7	Full	Yes	100%	100%
Wynn et al (2009)	18	Varied	Yes	100%	89% (93% for full-intensity conditioning)
For comparison BMT alone Boelens et al (2007)	146	Varied	No	85%	56%

Conclusions

- ERT improves patient airway and reduces cardiovascular compromise
- Intensive pre-transplant conditioning is possible because of better health of patients
- Combined ERT/HSCT results in decreased morbidity at the time of transplant, improved patient and graft survival.

Conclusions

Combined ERT/HSCT must now be regarded as the treatment of choice for MPS I patients aged less than 2 years.

However long term supervision is important as neither HSCT nor ERT can correct or completely prevent progression of the musculoskeletal complications of MPS, carpal tunnel compression or progressive corneal and retinal changes.

Combined ERT/HSCT for other MPS disorders

Combined ERT/ HSCT in a 3 year old girl with Maroteaux-Lamy syndrome, MPS VI.

At one year post ERT/HSCT treatment

- softening of facial features and hair, resolution of obstructive sleep apnoea and hepatosplenomegaly.
- improvement in hearing, joint range of movement, gross motor abilities and independence, although remains delayed for her age .

Urinary glycosaminoglycans and the N-acetylgalactosamine-4-sulphate sulphatase activity normal one year post treatment

A treatment regimen of ERT combined with HSCT in our patient with MPS VI provided similar benefit to patients with MPS I. This treatment regimen should be considered in the management of selected patients with MPS VI.

Poster # 108 COMBINED ERT and HSCT in MUCOPOLYSACHARIDOSIS TYPE VI

The Australian experience of combined ERT/HSCT for MPS disorders

To date 10 patients with MPS 1 and 1 patient with MPS VI have been treated with combined ERT/BMT in Australia

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