

## Clinical Updates in Paediatric BMT

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## Drugs Used in Conditioning Regimen

- Fludarabine + Busulphan + Melphalan + ATG
- Cyclophosphamide + total body irradiation
- Busulphan + Cyclophosphamide
- Carboplatin + Thiotepa + Etoposide
- Carmustine+ Etoposide+ Cytarabine + Melphalan

## Graf Versus Host Disease (GVHD)

- Acute GVHD – within 100 days post SCT
- A syndrome consisting of dermatitis, enteritis, and hepatitis
- Chronic GVHD usually develops after 100 days
- An autoimmune like syndrome consisting of impairment of multiple organs or organ systems.

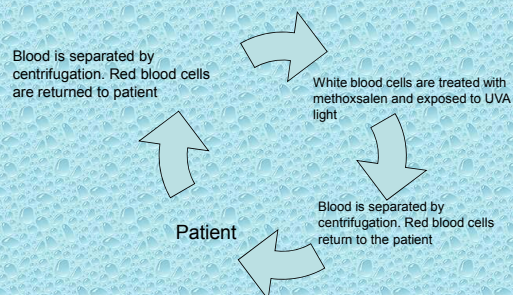
## Management of Acute GVHD

- Corticosteroid still the standard primary therapy - use in combination with Cyclosporin or tacrolimus
- In refractory cases the following agents are used:  
Mycophenolate mofetil  
Etanercept, Infliximab  
Denileukin diftitox  
Anti-thymocyte  
Rituximab

## Management of GVHD - ECP

- Extracorporeal photopheresis (ECP) is a therapeutic intervention which has demonstrated efficacy in patients with refractory acute and chronic GVHD.
- 3 basic steps in ECP:
  - 1) Leukapheresis
  - 2) Photoactivation
  - 3) Reinfusion

## Extracorporeal Photopheresis



## Management of Chronic GVHD -ECP

- Flowers ME, Apperley JF, van Besien K, et demonstrated that ECP improve skin GVHD significantly and allows lower doses of cortecosteroid to be used in the treatment of cGVHD in a randomised multicentre prospective phase II study

Flowers ME et al Blood 2008; 112(7):2667-74

## Management of Chronic GVHD

- Corticosteroid and cyclosporin – mainstay in cGVHD treatment
- Rituximab (Anti-CD20) in refractory cases
- Extracorporeal photopheresis ( ECP)
- Basiliximab
- Infliximab

## Veno-occlusive Disease (VOD)/ Sinusoidal Occlusive Syndrome (SOS) in Paediatrics

- Incidence ranges 1-31%
- Mortality approximately 50%
- Known risk factors include prior transplant, pre-existing liver disease, use of gemtuzumab ozogamicin, BUCY or melphalan containing regimen
- Recently sirolimus has been implicated

## VOD/SOS

- Clinical syndrome resulting from high dose myeloablative chemotherapy particularly in the setting of haematopoietic stem cell transplant
- Typically occurs 20 days post HSCT

## Characteristics of VOD/SOS

- Characterised by:
  - painful hepatomegaly
  - jaundice
  - ascites
  - fluid retention
  - weight gain

## Management of VOD/SOS

- No specific treatment modality for veno-occlusive disease (VOD) that could serve as a reference or criterion standard has been established.
- Studies on the use of many drugs to treat veno-occlusive disease are limited to case reports and small series.
- The primary goal of treatment is to normalize the flow in the sinusoidal vessels and veins by controlling the vasculitis and fibrin deposition

## Management of VOD/SOS

- **Supportive care**
- Prostaglandin E1 (PGE1) was investigated, but a prospective trial showed no convincing evidence beyond confirming the known considerable toxicities.
- Ursodeoxycholic acid was of no benefit in a prospective randomized trial.
- Antithrombin III (ATIII) was also studied only in small series or in combination with defibrotide.
- Additionally, none of these drugs demonstrated superior therapeutic efficacy.

## Defibrotide

- Polydisperse mixture of oligonucleotides derived from controlled depolymerisation of porcine intestinal mucosal DNA
- Appears to have local anti-inflammatory, anti-ischaemic, pro-fibrinolytic and anti-thrombotic actions
- Ability to modulate endothelial cell injury without systemic anti-coagulation effect

Morabito et al (2009) Expert Opinion Biol Ther 9(6): 763-772

## Defibrotide in the Treatment of VOD/SOS in Paediatric

- Corbacioglu S, Greil J, Peters C, et al. Defibrotide demonstrated that therapeutic efficacy upon early intervention in a retrospective multicentre study

## Defibrotide in the Treatment of VOD/SOS in Paediatric

- Corbacioglu et al retrospectively study of 45 children treated with Defibrotide
- 22/45 met criteria of severe VOD
- 76% of patients with CR and 64% with survival to day +100
- Of severe VOD, 50% CR and 36% survival at day +100
- Defibrotide tolerated with minimal toxicities

Corbacioglu S et al (2004) Bone Marrow Transplantation 33:189-195

## Defibrotide – VOD/SOS Prophylaxis

- Promising results from several small non-randomised trials
- Prospective Study of the Incidence and Outcome of Venoocclusive Disease (VOD) with the Prophylactic- Use of Defibrotide in Pediatric Stem Cell Transplantation.
  - phase II/III trial that intends to conclude if prophylactic defibrotide is superior to therapeutic defibrotide in children at high risk for developing veno-occlusive disease during stem cell transplantation
  - currently being conducted in Europe

## Defibrotide – VOD/SOS Prophylaxis

- 360 pediatric patients enrolled between January 2006 and January 2009
- from 28 centers in the European Union and Israel.
- 24% were infants, 52% were between the ages of 2 and 11 years, and 23% were adolescents.
- Approximately two thirds of patients (68%) underwent allogeneic stem cell transplantation and 31% underwent autologous stem cell transplantation.



### Defibrotide – VOD/SOS Prophylaxis

- Treatment arms:  
intravenous defibrotide 25 mg/kg daily, from the start of conditioning until 30 days after the transplant or until hospital discharge or the control group.  
All patients in the control group who were subsequently diagnosed with VOD received treatment with defibrotide.
- There were no significant differences between the 2 groups in disease types or risk factors.

### Defibrotide – VOD/SOS Prophylaxis

- The primary end point of the study was the incidence of hepatic VOD by day 30 using modified Seattle criteria (2 or more of the following: bilirubin >2 mg/dL, hepatomegaly, ascites, and unexplained weight gain of more than 5%)
- Secondary end points included mortality, morbidity, and the incidence and severity of GvHD.

### Defibrotide – VOD/SOS Prophylaxis

- In the intent-to-treat analysis, 12% (22 of 180) of the patients in the defibrotide group and 20% (35 of 176) of those in the control group developed VOD by day 30 ( $P = .054$ )
- Mortality of patients with VOD at day +100 was 24.6% vs 6% in patients without VOD ( $P < .0001$ ).

### Defibrotide – VOD/SOS Prophylaxis

- The use of prophylactic reduced the incidence of VOD in the intent-to-treat analysis of all randomized patients by 40% (from 20% to 12%).

### Defibrotide – VOD/SOS Prophylaxis

- The incidence of renal failure was reduced to 1% compared with 6% in the control group
- VOD mortality was also reduced 6% to 2%
- The overall incidence and severity of acute GvHD were significantly lower in the defibrotide group (32% vs 43%)

### Vaccination

- Protective immunity to vaccine-preventable diseases is partially or completely lost following either allogeneic or autologous stem cell transplantation
- Impaired immunity following allogeneic transplantation is caused by a combination of the preparative chemotherapy given before transplantation, graft-versus-host disease (GVHD), and immunosuppressive therapy following transplantation.

## Vaccination

- Routine vaccination after HSCT provided patient is off immunosuppressive therapy and do not suffer from GVHD
- Immunisation with :
  - nonliving vaccines at least 12 months after HSCT
  - live attenuated vaccines 24 months after HSCT
  - life long seasonal influenza vaccines for all candidates and recipients beginning during the influenza season before HSCT and resuming 6 months after HSCT

European group for Blood and Marrow Transplantation (EBMT), Centers for Disease Control and Prevention\*, Infectious Diseases Society of America\*, and American Society of Blood and Marrow Transplantation

## Recommended Vaccinations for Post Stem Cell Transplant Patients

Current Opinion in Infectious Diseases 2008; 21:399-408

Vaccines	Schedule
Tetanus/diphtheria/acellular pertussis	12, 14-16 and 24 months
Pneumococcal (conjugated seven valent)	12, 14-16 and 24 months
Haemophilus	12, 14-16 and 24 months
Influenza	≥ 6 months post SCT; annually
Inactivated polio	12, 14-16 and 24 months
Measles –mumps – rubella	24 months ( if no significant GVHD and minimal immunosuppression)
Varicella	Contraindicated at this time
Hepatitis B	12 months +, first dose + 2 months, first dose + 6 months 12+
Hepatitis A	12months +, first dose + 6-12 months
Meningococcal (conjugated)	12 months +
Typhoid Vi polysaccharide	One dose ≥ 2 weeks prior to travel

## Human Cytomegalovirus Vaccination

- *Tobias Feuchtinger et al, University Children's Hospital, Eberhard-Karls University, Tübingen, Germany*
- Dendritic cell vaccination in an allogeneic stem cell recipient receiving a transplant from a human cytomegalovirus (HCMV)-seronegative donor: induction of a HCMV-specific T helper cell response

## Pneumococcal Vaccination

- 1 dose of 23 valent –polysaccharide pneumococcal( PCV23) dose after 3 doses of 7 valent
- known to increase the response to PCV7, also extends the serotype coverage given 12 or 18 months after transplant  
Pneumococcal vaccine 7 valent

## Summary

- No clear standard for salvage treatment in steroid refractory aGVHD
- Supportive care is still the mainstay in the management of cGVHD
- No definitive viable treatment available in preventing SOS/VOD but defibrotide shows promise
- Vaccination post transplant is as per current guidelines