FULMINANT EBV –ASSOCIATED HAEMOPHAGOCYTIC SYNDROME FOLLOWING UNRELATED STEM CELL TRANSPLANTATION. REPORT OF A CASE FROM JULES BORDET INSTITUTE.

Clinical features

- 66 years old man, chemical engineer.
- 2011 AML secondary to MDS, normal Karyotype, Negative WT1.
- Treatment:
  - cytarabine + idarubicin → partial remission
  - HD Cytarabine + Amsacrine → CR
  - Mitoxantrone + cytarabine
- 02/2013: relapse with normal karyotype, negative WT1.
- Treatment:
  - Reinduction → CR
  - Consolidation ID aracytine → Transplant was delayed: Anal abcess
- Donor: Male 38yo, MUD 10/10, CMV +/-, Rhesus incompatibility.
Predictive scores

- HCT-CI at 2, EBMT score at 5 → NRM at 28%, OS at 53%
Early 100 days

- Conditioning regimen: RIC
  - Busulfan, ATG, Fludarabine
  - GVHD prevention: Tacrolimus and sirolimus
- HSCT: $5.95 \times 10^6$ CD34+/Kg, $1.1 \times 10^8$ CD3+/Kg, $3.87 \times 10^8$ WBC/Kg

- Aplasia: Febrile neutropenia + sinusitis $\Rightarrow$ antibiotics
- Engraftment: Day +24
Early 100 days

• Day+33: Fever at 40, chills, tachycardia, dyspnea, moderate kidney failure, hepato-splenomegaly

• Biology:
  o Pancytopenia: secondary engraftment failure,
  o Hyperferritinemia: 29480ug/l
  o Triglycerids: 639mg/dl
  o LDH: 2400IU/l
  o Liver dysfunction GOT/GPT=657/200
  o Kidney failure.
  o Hemophagocytosis on bone marrow

• Microbiology:
  o EBV PCR at 4463476 copies

• Medullar Immunophenotyping:
  o 65% of population CD3+ CD8+ express TCR A/B+ CD7+ CD1a- CD28+ tdt –
  o Balance CD4/CD8= 0.1

• **FULMINANT EBV –ASSOCIATED HAEMOPHAGOCYTIC SYNDROME**
Evolution

- Transfer to ICU for MOF
- Treatment:
  - Rituximab 375mg/m2 and corticosteroids. Etoposide was not given. Sirolimus and tacrolimus were stopped ➔ decreasing of LDH, Tg, ferritinemia.
- Evolution: Increasing liver dysfunction
  - Liver biopsy: GVHD steroids refractory ➔ ATG
- Death ➔ sepsis and MOF
Diagnosis criteria of HPS

**Major criteria**

1. Engraftment failure, delayed engraftment, or secondary engraftment failure after HSCT
2. Histopathological evidence of haemophagocytosis

**Minor criteria**

1. High grade fever $>38.5$°C
2. Hepato-splenomegaly
3. Elevated ferritin $>500$ng/ml
4. Elevated serum lactate dehydrogenase (LDH)

Cytopenia has been excluded in post HSCT

Diagnosis = 2 major criteria or 1 major criterion + 4 minor

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Physiopathology

**Int J Hematol 2004; 80: 467–469**

- Defective killing mechanism
- Infection
- Activated tissue macrophage (histiocyte)
- Cytokines

Karras et al / Actualités néphrologiques 2005

**Bone Marrow Transplantation (2007) 40, 701–703**

- Residual host-derived macrophages were involved in the development of allo-HSCT-associated HPS. The early onset-allo-HSCT-associated HPS as a form of host-versus-graft response (in JMML patients)

**Transplantation 2002; 73: 104-111**

- Macrophage population remains chimeric until 3 months after HSCT (even after MAC)
Incidence

+ 25 patients in 17 case reports after autologous \((n = 5)\) and allogeneic \((n = 21)\) HSCT. Among 21 patients who received allogeneic HSCT, RIC \((n=9)\), CBT\((n=5)\). HPS has been considered as a rare event after HSCT.

+ HPS is known to occur early (during weeks 2–6) after allo-HSCT

+ Abdelkafi et al (Int J Hematology 2009) published a prospective observational study on 171 patients who underwent HSCT (68 allogenic and 103 autologus). He observed 6 cases of HPS. Incidence was 8,8%. 3 cases were caused by viral infections.

+Kobayashi et al (Bone Marrow Transplant 2014) studied 554 patients with HPS after HCT . The cumulative incidence was 4,3%.

Fewer infused CD34+ cells is a significant risk factor for the development of HPS (p=0.01). The incidence of HPS was higher in the ‘reduced-intensity’ group, although it did not reach statistical significance (P = 0.17).

The Use of etoposide in the conditioning regimen was the only factor that reduced HPS after SCT (p=0.027)

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Prognosis

• The prognosis is poor and the mortality is high.
• Patients with liver dysfunction had a poor response to treatment.
• Takagi et al found 85% of mortality in patients with HPS after allogenic HSCT. The cause of mortality: sepsis (41%), relapse (17%), GVHD (15%), Hemorrhage (12%)
• OS at 4 years was significantly poorer in patients with HPS.

15.0% vs. 35.4%;
P = 0.0002

Bone Marrow Transplant (2014) 49 (2), 254-7
British Journal of Haematology (2009), 147, 543–53
Treatment

- Treatment of the cause
- Etoposide
- Corticosteroids
  - Cyclosporin A inhibits T lymphocytes
- IGIV
- ATG
- Bone marrow or stem cell transplantation
- Anti TNF alpha Ab

Karras et al / Actualités néphrologiques 2005
Chinese Medical Journal 2013;126(18):3587-3589
Conclusions

• HPS following HSCT is a rare fatal event.
• Mostly caused by viral infection.
• Predictive score for HPS before HSCT
• The origin of macrophages is still controversial
• Risk factors: amount of CD34+, RIC, Etoposide.
• Bad prognosis, high mortality.
• Treatment of the cause + etoposide (controversial) + steroids

Thank you for your attention