Joint Educational Meeting of the EBMT
Severe Aplastic Anaemia, Late Effects and
Autoimmune Diseases Working Parties

10.30-11.00 Late liver complications Dr Enric Carreras
Late liver complications after SCT

- Chronic GvHD
- Chronic viral hepatitis and cirrhosis
- Hepatocellular carcinoma
- Iron overload
- Nodular regenerative hyperplasia
- 1-2 clinical cases
Chronic GvHD of the liver
• Incidence:
  – 30% (HLA= sibling) to 80% (UNR 7/8)

• Time of onset:
  – Day +150 (median); exceptional (5%) >1 year (if not DLI)

• Usually associated with other manifestations of chronic GvHD

Strasser & McDonald, Thomas’ HCT, 2009
Clinical forms

- **Cholestatic:**
  - ↑ FA and γGT, asymptomatic

- **Icteric:**
  - Damage to or loss of small bile ducts from ductopenia to vanishing bile duct syndrome (VBDS)

- **Hepatitic GvHD:**
  - AST/ALT > 2,000 U/L usually in patients w/o or w minimal immunosuppression (or receiving DLI)

*Strasser & McDonald, Thomas’ HCT, 2009*
Diagnostic

• Cholestatic / Icteric forms:
  – Usually no additional explorations are needed; easy diagnosis if other organs with GvHD
  – VBDS: after SCT no other pathologies with persistent bilirubin >20 - 30 mg/dL

• Hepatitic:
  – Liver biopsy is needed to exclude other possible causes
  – Possible auto/allo antibodies (CYP1A2, LKM,...)

Strasser & McDonald, Thomas’ HCT, 2009
Treatment

• Cholestatic form:
  — Usually do not require treatment, specially if the liver is the only affected organ

• VBDS:
  — Symptomatic treatment (cholestyramine, UDCA)
  — Once established, poor response to immunosupp., may persist for months-years

• Severe forms (hepatitic or icteric):
  CNI + PDN ± UDCA

• Liver transplantation (exceptionally performed)

Strasser & Mc Donald, Thomas’ HCT, 2009
Chronic viral hepatitis, cirrhosis and hepatocellular carcinoma
Causes of hepatitis after SCT

- Hepatitic GvHD
- VZV, CMV, EBV hepatitis (infrequent)
- VB and VC hepatitis
- Drug induced hepatitis
  - Antihypertensive drugs
  - Lipid-lowering agents
  - Hypoglycemic agents
  - Nonsteroidal anti-inflammatory agents
  - Antidepressants
  - Antibiotics

High incidence of metabolic syndrome
Psychiatric dist.
Infections
**Chronic hepatitis by VBH**

<table>
<thead>
<tr>
<th>Events</th>
<th>HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>3 - 4% EU</td>
</tr>
<tr>
<td>Patient sero (+)</td>
<td>SCT not contraindicated</td>
</tr>
<tr>
<td>Donor sero (+)</td>
<td>SCT not contraindicated</td>
</tr>
<tr>
<td>Transmission Don → Rec</td>
<td>30 – 50%</td>
</tr>
<tr>
<td>Sinusoidal obstruction syndr.</td>
<td>no ↑ incidence</td>
</tr>
<tr>
<td>Risk of fulminant hepatitis</td>
<td>5 – 15 % *</td>
</tr>
<tr>
<td>Risk of hepatic GvHD</td>
<td>= Incidence</td>
</tr>
<tr>
<td>Hepatitis post-SCT (3 – 5 m)</td>
<td>up to 75% **</td>
</tr>
<tr>
<td>Long term evolution</td>
<td>occasional flares of hepatitis</td>
</tr>
<tr>
<td>Evolution to cirrhosis</td>
<td>Exceptional</td>
</tr>
<tr>
<td>Antiviral treatment</td>
<td>lamivudin / entecavir / tenofovir</td>
</tr>
<tr>
<td>Survival at 10 years</td>
<td>no impact</td>
</tr>
</tbody>
</table>

- Specially if pre-core HBV mutant (HBsAg+, anti-HBc+, antiHBe+, DNA +/-)
- Specially when reducing immunosuppression

How I treat... Llang R. Blood 2009

Carreras et al., Yellow Book on SCT, 2010
# Chronic hepatitis by HCV

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<td>possible chronic hepatitis</td>
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<tr>
<td>Evolution to cirrhosis</td>
<td>24% at 20 years *</td>
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<tr>
<td>Antiviral treatment</td>
<td>Pegylated IFN ± ribavirin</td>
</tr>
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<td>Survival at 10 years</td>
<td>no impact</td>
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*Not all authors agree*

*If RNA VCH +*

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*Carreras et al., Yellow Book on SCT, 2010*
2-8% of hepatocellular carcinoma per annum (also more NHL and other LPD)

Cause?
GvHD? Iron overload? immunosuppression?

Evolution of chronic hepatitis by VCH after SCT

Peffault de Latour et al., Blood 2009
Chronic hepatitis by HCV

Probability of dying due to liver complications

5.8% allogeneic
6.4% autologous

Ljungman et al., (in press)
# Chronic hepatitis by HCV

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**Carreras et al., Yellow Book on SCT, 2010**

**P- INF:** Possible rapid falls in platelet and granulocyte counts; Risk GvHD reactivation

**Ribav:** Haemolysis

**Evolutionary control**
- ALT > AST → AST > ALT
- Alfafetoprotein
- Ultrasounds/FibroScan (fibrosis index)
Iron overload
Iron overload

• Up to 88% of long term survivors
• Produced by prolonged dyserythropoiesis, increased iron absorption, transfusions
• Iron accumulates in liver, myocardium,.....
• Well known effects:
  — Contribute to: hepatic fibrosis, cirrhosis and hepatocellular carcinoma; cardiac dysfunction; higher incidence of mucormycosis
• Other possible effects
  — Diabetes, impotence, hypogonadism, growth retardation

*Socié et al., Blood 2003; Strasser & McDonald, Thomas’ HCT, 2009*
Iron overload

• Diagnosis:
  — Serum ferritin >1,000 μg/dL (not evaluable in patients with chronic GvHD or any liver disease)
  — Liver biopsy or MRI / FerriScan

• Treatment:
  — Phlebotomy (≈ 400mL every 3-4 weeks) up to ferritin <700. Associated with EPO if necessary
  — Chelating agents, effective but expensive
  — Erythroaphereses, expensive, usually not necessary

Socié et al., Blood 2003; Strasser & McDonald, Thomas’ HCT, 2009
Nodular regenerative hyperplasia
Nodular regenerative hyperplasia

• Occasionally observed in patients with haematological malignancies (MPD, CLL, CML, NHL)

• After SCT in patients with a previous VOD/SOS

• Probably consequence of changes in hepatic blood flow

• Atrophy of zone 3 of the acinus and hypertrophy of zone 1 (without fibrosis)
Nodular regenerative hyperplasia

• Clinical manifestations:
  – Silent evolution (only ↑ FA) unless portal hypertension develops (ascites, splenomegaly, thrombocytopenia)

• Diagnosis
  – Suspected by imaging (MRI)
  – Liver biopsy to rule out carcinoma and cirrhosis; NRH needs a wedge biopsy (avoid tranjugular approach or small needles)
Late liver complications after SCT

Take care of me!
Clinical case 1

• 40 yo. Allo-RIC unrelated x AML
• On day +3 mild VOD – resolved with diuretics
• + 150: Jaundice, ascites, encephalopathy
• Bilirubin 22 mg/dL, FA 1.400 UI, ALT: 450; Ferritin: 7.000 µg/dL
• Liver Bx: hemosiderosis, moderate ductopenia
• Low dose PDN, UDCA, cholestyramine, diuretics
• Phlebotomies + EPO
• Slowly recovery, normal liver tests, Ft: 500µg/dL
Clinical case 2

- 50 yo. 2on SCT (allo-MAC) due to CML (1995). HCV at SCT
- 10 m after: Chronic GvHD (oral, ocular, hepatic, obliterans bronchiolitis)
- FA: 750 mg/dL, GGT: 600 mg/dL, ALT: 80; platelets 85,000; Ferritin: 4,050 µg/dL
- CsA+PDN: slowly improvement of cGvHD
- 16 m SCT w/o PDN: Diabetes insulin dependent
- Phlebotomies every 3-4 weeks
- After 16 phleb → Normal glycaemia w/o insulin
Many thanks for your attention.