Systemic sclerosis and graft-versus-host disease: similarities and differences
The HSCT expert’s perspective

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Outline of Presentation

• GvHD: Background
• Differences
  – Graft versus Malignancy
  – Variation in clinical features
• Similarities
  – Multidisciplinary approach
  – Consensus opinion
  – Unmet clinical needs
    • Challenges of conducting clinical trials
    • Similar treatment paradigms
Graft versus Host Disease: Incidence

• **Acute GvHD**
  – Incidence of 35-45% in sibling transplants
  – 60-80% in one antigen mismatched unrelated donor grafts

• **Chronic GvHD**
  – Incidence of 30-80%

• **Increasing incidence**
  – More unrelated donor transplants
  – Patients receive peripheral blood
  – Reduced intensity conditioning for older patients
  – Use of donor lymphocyte infusions
GvHD syndrome after allotransplant

Day 0

Acute GvHD

Overlap syndrome + Late onset Acute GvHD

Years post Transplant

Classic Chronic

Skin rash
Jaundice
Diarrhoea

Skin, eyes, mouth, lungs, GU, liver, Musculoskeletal, GI
Graft versus Malignancy

GVHDとGVL効果のバランスをとるのは難しい
Acute GvHD
Chronic Skin GvHD

sclerodermoid

lichenoid
Sclerodermoid GvHD
Other manifestations
Clinical manifestations of systemic sclerosis

- Skin sclerosis
- Inflammation
- Vasculopathy
- Emotional
- Financial
- Social
- Pain
- Exocrine
- Pulmonary
- Cardiac
- Gastrointestinal
- Renal
- Digital ulceration
- Musculoskeletal
- Macrovascular disease

Shown with permission
Key differences

- Variation in clinical features
- GvHD is directly related to transplant procedure
- Graft versus malignancy effect
- Survivorship
Similarities: Multidisciplinary approach

Worldwide support for people with scleroderma, Scleroderma Society
MDT approach

Scleroderma Society

SSc/GVHD Patient

Family

Pharmacist

Friends

OT/Physio

Medical specialists

Nurses

Work

EBMT patient & Family Day
MDT approach

• Close collaboration between specialties
• Importance of key worker e.g. CNS
• Role of specialist centres/dedicated clinics
• Continuity of care
• Allows development of expertise
• Enables clinical research
Similarities: Consensus opinion

GVHD
• BCSH/BSBMT guidelines
• European consensus reports
• NIH working parties
• EBMT working party

Systemic Sclerosis
• UKSSG
• EULAR recommendations
Consensus opinion – GVHD

In patients who fail one 2\textsuperscript{nd} line therapy, another 2\textsuperscript{nd} line agent should generally be used before moving to 3\textsuperscript{rd} line options

1\textsuperscript{st} Line Treatment: 1mg/kg oral prednisolone (1B)

2\textsuperscript{nd} Line: 1B
ECP (Skin, mouth, liver)

2\textsuperscript{nd} Line: 2C
M-tor inhibitor

2\textsuperscript{nd} Line: 2B
Rituximab (Skin, Musculoskeletal)

2\textsuperscript{nd} Line: 2B
Pentostatin

2\textsuperscript{nd} Line: 2C
Imatinib (Sclerodermoid skin, lung)

Calcineurin inhibitor as steroid sparing agent (2C)

Enrol in clinical trial if available

Methotrexate

Pulsed Corticosteroids

Mycophenolate Mofetil

Third Line Options (2C)

BCSH/BSBMT cGVHD guideline, BJH, 2012
Consensus opinion – systemic sclerosis

• SSc-related skin involvement
  – Two RCT have shown that methotrexate improves skin score in early diffuse SSc. Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc (A)

• SSc-ILD
  – In view of the results from two high-quality RCT and despite its known toxicity, cyclophosphamide should be considered for treatment of SSc-ILD (A)

Kowal-Biekecka et al, EULAR recommendations, Ann Rheum Dis 2009
Similarities: Clinical challenges

GVHD
- Skin ulcers
- Steroid-refractory gut GvHD
- Psychological and emotional impact
- Physical limitations
- Pulmonary GvHD

Systemic Sclerosis
- Digital ulcers
- Anorectal incontinence & malnutrition
- Psychological and emotional impact
- Physical limitations
- Calcinosis

Both conditions remain life threatening & cause considerable morbidity
Similarities: Clinical trials - challenges

- Response criteria
- Recruitment
- Toxic agents
- Require multicentre collaboration
## Similarities: Targeted therapies SSc

<table>
<thead>
<tr>
<th>Candidate therapy</th>
<th>Target pathway</th>
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<tbody>
<tr>
<td><strong>Bosentan</strong></td>
<td>$\text{ET}_A/\text{ET}_B$ receptor</td>
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<tr>
<td><strong>Ambrisentan</strong></td>
<td>$\text{ET}_A$ receptor</td>
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<td><strong>Selexipag</strong></td>
<td>IP receptor agonist</td>
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<td><strong>Infliximab, Adalimumab</strong></td>
<td>TNF$\alpha$ ligand</td>
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<tr>
<td><strong>Etanercept</strong></td>
<td>TNF$\alpha$ ligand</td>
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<td><strong>Rituximab</strong></td>
<td>CD20</td>
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<td><strong>Basiliximab</strong></td>
<td>IL-2R$\alpha$</td>
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<td><strong>MLM-1202</strong></td>
<td>CCR2</td>
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<td><strong>Efalizumab</strong></td>
<td>LFA1/ICAM-1</td>
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<td><strong>Tocilizumab</strong></td>
<td>IL-6R</td>
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<tr>
<td><strong>Abatacept</strong></td>
<td>CTLA4</td>
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<tr>
<td><strong>Imatinib, Dasatinib</strong></td>
<td>TGF$\beta$1</td>
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<tr>
<td><strong>Nilotinib</strong></td>
<td>TGF$\beta$1,-$\beta$2,-$\beta$3</td>
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<tr>
<td><strong>c-Abl, c-Kit, PDGF</strong></td>
<td>CTGF ligand</td>
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<td><strong>CAT-192</strong></td>
<td>TGF$\beta$ ligand (topical)</td>
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<td><strong>GC-1008</strong></td>
<td>VEGF, bFGF, PDGF</td>
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<td><strong>FG-3019</strong></td>
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Agents in red also used in GvHD
Conclusions

• Both conditions face similar challenges
• MDT working essential
• Consensus opinion useful
• Unanswered questions remain
• Clinical trials essential but challenging
Acknowledgements

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