RIC Allogeneic transplant vs. Myeloablative allogeneic transplant for Elderly (>55yr) High Risk AML

David Brittain
Clinical Haematologist
Faerie Glen Hospital
Pretoria
• A 55 years old man with adverse karyotype AML (monosomy 7) and no co-morbidities has an HLA identical sibling. The patient has inquired if you would opt for full intensity or RIC allografting?
Rationale of conditioning

• Treat the underlying disease
• “Clear the way”
• Prevent rejection (immunosuppression of the host)
• Prevent/modify GvHD (immunosuppression of the Graft)
Myeloablation

- Busulfan 16mg/kg PO or 12.8mg/kg IV
- Whole body irradiation 11-14 Gy
- Combined with either above, Cyclophosphamide 120-200mg/kg
What is Reduced Intensity Conditioning?

• Anything less than full myeloablation
• Any attempt to reduce toxicity of chemotherapy or radiation
• Any immune manipulation or modulation
• Incorporation or “piggy-backing” of disease specific therapies and conditioning
Reduction of toxicity

- Reducing dose of busulfan or radiation
- Alternate immunosuppression: e.g., changing cyclophosphamide to fludarabine
- Use of alternate myeloablative drugs: e.g., intermediate dose melphalan
- Pharmacologic dosing: maintaining steady state plasma levels of busulfan
Immune manipulation or modulation

- Acute-GvHD increases TRM
- Direct T-cell antagonists such as anti-thymocyte globulin, alemtuzumab, daclizumab in addition to cortico-steroids, methotrexate and cyclosporine/tacrolimus/mycophenolate mofetil
- Given in-vivo prior to or during the transplant vs. into the graft (in-the-bag)
- Have less effect on chronic-GvHD
- Chronic GvHD reduces incidence of relapse
Piggy-backing

- Disease specific agents such as Gemtuzumab Ozogamicin, imatinib and farnesyl transferase inhibitors
- Have less toxicity than conventional cytotoxics
- Allow better disease control, buying time for GvL effect
- Eradicate minimal residual disease
Why RIC?

- Efficacy of allogeneic haemopoietic stem cell transplant in the eradication of malignant disease
- Provide access to HST for patients with co-morbidities or advanced age who have an increased TRM from conventional myeloablation
- Disease demographics: increased incidence of AML/MDS in older patients and worse prognosis disease in these patients
- In some diseases GvL effect is important and especially if MRD
- Allows the use of alternative donor/stem cell sources e.g. MUD’s & UCB
Why not RIC

• Some diseases need the chemotherapy or radiation dose (myeloablative dose)
• Active or progressive disease
• Refractory disease
Acute Myelogenous Leukemia
Survival of Older Adult (Age ≥ 55 Years) Marrow and PBSC Recipients with Non-Myeloablative Preparative Regimens, by Disease Stage 1998–2006

Log-rank p-value = 0.0002

- Second complete remission (n = 107)
- First complete remission (n = 239)
- Advanced (n = 113)

Years After Transplant

NATIONAL MARROW DONOR PROGRAM®
Acute Myelogenous Leukemia
Survival of Older Adult (Age ≥ 55 Years) Marrow and PBSC Recipients with Myeloablative Preparative Regimens, by Disease Stage 1998–2006

Log-rank p-value = 0.009

First complete remission (n = 82)
Second complete remission (n = 44)
Advanced (n = 69)

Years After Transplant
Survival
0 1 2 3 4 5
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

NATIONAL MARROW DONOR PROGRAM®
Myelodysplastic Syndromes
Survival of Adult (Age ≥ 18 Years) Marrow and PBSC Recipients with All Preparative Regimens, by Age at Transplant 1998–2006

Log-rank p-value = 0.03

Age 18–54 Years (n = 289)
Age ≥ 55 Years (n = 163)

NATIONAL MARROW DONOR PROGRAM®
Myelodysplastic Syndromes
Survival of Adult (Age ≥ 18 Years) Marrow and PBSC Recipients with RAEB/RAEB-T by Conditioning Regimen 1998–2006

Log-rank p-value = 0.11

Myeloablative (n = 305)
Non-myeloablative (n = 147)

Years After Transplant

Survival

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
0 1 2 3 4 5

NATIONAL MARROW DONOR PROGRAM®
Case assumptions

• The patient is in CR
Decision

• This patient without significant co-morbidity but high risk disease can have a RIC allogeneic transplant because:
  • He is in CR
  • Age

• However I would concentrate on modifying the toxicity and on reducing the A-GvHD risk rather than reducing the dose intensity of the ablation
  • i.e. busulfan IV 6,4mg-8,6mg (or plasma level adjusted)
  • Substitution of cyclophosphamide by fludarabine
  • Addition of melphalan
  • T-cell modulation