Mini Stem Cell/Bone Marrow Transplantation.

Clinical Area: Mini stem cell/bone marrow transplantation.
Keywords: Hematologic malignancies, older patients, hematopoietic cell transplantation, graft-versus-tumor.

Study Type: Case Series.
Study Aim: To report the results of hematopoietic cell transplantation (HCT) using low dose total body irradiation/mycophenolate mofetil/cyclosporine (TBI/MMF/CSB) among patients with hematologic malignancies who were ineligible for conventional HCT because of age or medical contraindication, and with HLA-identical sibling grafts.

Outcomes:
- **Primary**: Mixed chimerism (between 1% and 95% peripheral blood {PB} donor cells) at day 28.
- **Secondary**: Acute and chronic graft-versus host disease (GVHD), and tumor response.

Design:
- **Number of subjects**: N=45. (n=32 outpatient transplantation, and n=13 inpatient transplantation).
- **Method of subject selection (inclusion/exclusion criteria)**: Inclusion: Indolent hematologic malignancy or acute leukemia in complete remission (CR), HLA identical sibling with serologic match, age >50 years (>60 for CML) or relative contraindication to conventional HCT in younger patients, creatinine clearance >50 mL/min, bilirubin less than two times normal, and Karnofsky score >50. Additional inclusion criteria were failing at least frontline therapy for CLL and lymphoma patients, and Stage II or II at diagnosis for multiple myeloma (MM) patients.
- **Consecutive patients?** Yes.
- **Description of study population**: Study subjects were patients treated at Fred Hutchison Cancer Research Center, UW medical Center, VA Medical Center in Seattle, Stanford University, and The University of Leipzig in Germany between December 17, 1997, and May 27, 1999. Thirty one (68.9%) patients were men and 14 (31.1%) were women, with an age of 31 to 72 years. More than half (57.8%) of the patients were 55 years of age or older, 9 (20%) were between 50 and 55 years of age, and 10 (22.2%) were <50 years old. 11 (24.4%) patients had AML, 9 (20%) had CML, 8 (17.8%) had CLL, 4 (8.9%) had Hodgkin disease, and the rest had other hematologic malignancies. All patients but one had used a previous regimen, and 7 (15.5%) had undergone a previous autograft.
- **Exposure/Intervention**: 44 patients received 2 Gy TBI (total body irradiation) alone, and only one patient with CML received an additional fludarabine before the HCT. Prophylaxis was given against Pneumocystis carinii, fungal infections, and cytomegalovirus. Patients with chronic GVHD received antibiotic prophylaxis against P carinii and pneumococcus. Patients received immunosuppression with CSP/MMF after the transplant. Patients with mixed chimerism, no GVHD, and <20% increase in donor T cells from day 28 to 56 were eligible for donor lymphocytic infusions (DLIs) on day +65. In the others monthly chimerism and tumor evaluations were done to assess the need for DLI.
- **Source of outcome data (e.g. patient self-report, doctor report, lab results)**: Outpatient transplantation patients had scheduled clinic visits 2-3 times per week for the first month and then 1-2 times per week or as required thereafter. Chimerism among peripheral blood T cells, granulocytes, and unfractioned marrow was assessed at days 28, 56, 84, 180, and 360 after HCT. Tumor response was evaluated, and acute and chronic GVHD were assessed and graded.
- **Length of follow-up**: 310-769 days with a median of 417 days.
- **Completeness of follow-up**: Some follow-up on all patients.
Validity:
- *Is the study type appropriate for the question(s) being asked?* A randomized controlled trial would be ideal, but apparently is not an option among these patients, who are not candidates for the conventional transplantation.
- *Were patients similar with respect to baseline characteristics?* They all had hematologic malignancies, and a contraindication for conventional HCT.
- *Was the intervention and other aspects of patient care similar for all patients (or for all patients in a defined subgroup)?* Yes.
- *Was the process of observation likely to affect the outcome?* Probably not.
- *Did an objective observer assess outcomes and were outcome measurements consistent?* Yes.
- *Was follow-up duration appropriate?* Not for all patients.
- *Was follow-up rate sufficient?* Yes.

**Conclusions regarding validity of methods:**
This case series had some advantages: It included consecutive patients, had well defined inclusion criteria, and objective outcomes. However, it had a small sample size, a variable duration of follow-up (310-769 days), and no control or comparison group.

**Results:**

<table>
<thead>
<tr>
<th>Median percent and chimerism status</th>
<th>Day 28 (n=44)</th>
<th>Day 56 (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median % (range) of donor cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T cells</td>
<td>60% (10-100)</td>
<td>90% (5-100)</td>
</tr>
<tr>
<td>Peripheral blood neutrophils</td>
<td>91% (0-100)</td>
<td>99% (4-100)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>87% (0-100)</td>
<td>95% (2-100)</td>
</tr>
<tr>
<td>Chimerism based on T cells engraftment</td>
<td>86%</td>
<td>79%</td>
</tr>
<tr>
<td>Mixed</td>
<td>14%</td>
<td>21%</td>
</tr>
<tr>
<td>Full donors (complete)</td>
<td></td>
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</tr>
</tbody>
</table>

**Graft rejection**
9 (20%) of the 44 patients who received TBI/CSP/MMF had graft rejection between 2 –4 months.

**Acute GVHD (n=36 patients with sustained allografts)**
- Developed acute GVHD: 17/36 (47%)  
  - Grade II: 13/36 (36%)  
  - Grade III: 4/36 (11%)  
- No acute GVHD: 19/36 (53%)

**Chronic GVHD (n=31 patients were evaluable)**
- Developed chronic GVHD*: 23/31 (74%)  
- No chronic GVHD: 8/31 (26%)

* 19 were treated with systemic immunosuppressive therapy, one with topical steroids, and three received no specific therapy.
Survival at a median follow-up of 417 days (range 310-769):

N=45
Survivors 30 (66.7%)
Deaths 15 (33.3%)
Due to progressive disease 12 (26.7%)
Due to transplantation complications* 3 (6.7%)

* Pneumonia, CNS hemorrhage, and streptococcal infection after sinusitis.

Outcome of disease

N=45
Complete remission 14 (31.1%)
Molecular remission 8 (17.8%)
Partial remission 3 (6.7%)
Untreated relapse 6 (13.3%)
Progressive condition 12 (26.7%).
Stable condition 2 (4.4%)

Patients who died were in progressive condition, or in remission with infection.

Adverse events

Serum creatinine elevation (2 x baseline value) 59%
Hyperbilirubinuria>10mg/dL 7%
Bacterial infections requiring IV antibiotics 22%
CMV reactivation 24%

None of the patients experienced any painful mucositis, severe nausea and vomiting, pulmonary or cardiac toxicity, hemorrhagic cystitis, or new onset alopecia.

Authors' Conclusions:

The authors concluded that the use of postgrafting immunosuppression to control graft rejection and GVHD reduces the acute toxicities of allografting considerably. They also concluded that with the induction of potent graft-versus tumor effects, HCT may be conducted among previously ineligible patients, and can be performed in an outpatient setting.

Reviewer’s Conclusions:

This case series found a relatively high survival, and remission rate among patients with hematologic malignancies who received hematopoietic cell transplantation (HCT) using low dose TBI/MMF/CSB. However, due to the study design, it is not possible to determine whether this intervention is more effective than no intervention, or an alternative intervention if any is available for these patients ineligible for conventional HCT because of age or other medical contraindication.