

Transplantation of 'Rainy Day' Autologous Peripheral Blood Stem Cells

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Introduction

High-dose myeloablative therapy in conjunction with Autologous Peripheral Blood Stem Cell (APBSC) transplantation is being used with increased frequency to treat a range of haematological malignancies including Multiple Myeloma (MM), Non-Hodgkin Lymphoma (NHL) and Acute Myeloid Leukemia (AML). With sufficient resources, APBSCs can be harvested in patients during remission or consolidation treatment for subsequent transplantation if required ('Rainy Day' collection). We investigated the eventual transplantation of Rainy Day collections at our centre to assess the utilisation of this strategy.

Methods

APBSCs were collected, processed and stored in accordance with the code of Good Manufacturing Practice (cGMP) in a Therapeutic Goods Administration (TGA) licensed facility at the Centre for Blood Cell Therapies (CBCT), Peter MacCallum Cancer Centre. APBSCs were cryopreserved in 10% DMSO with a final nucleated cell concentration of $200 \times 10^6/\text{mL}$.

Results

Transplantation of 'Rainy Day' Autologous PBSC

- Over a 6 year period (January 2001 – December 2006), we collected 365 out of total of 728 patients (50%) for 'Rainy Day' storage (Refer to Figure 1).
- Primary disease indications for Rainy Day collections included NHL (45%, n=166), MM (12%, n=44), AML (8%, n=29) and Chronic Myeloid Leukemia (CML) (7%, n=25).
- Rainy Day storage constituted 53% of all NHL collections (n=166/309), 23% of MM (n=44/202), 86% of AML (n=29/34) and 100% of CML collections (25/25).
- To date, over 23% (n=84) of these Rainy Day collections have resulted in transplantation (Refer to Figure 2).
- NHL has accounted for the majority of these transplants (47%), followed by MM (27%), AML (8%), Acute Lymphoblastic Leukemia (ALL) (4%), Hodgkin Lymphoma (HL) and Chronic Lymphocytic Leukemia (CLL) (4%).
- By contrast, CML has resulted in one transplant, 1% of all Rainy Day transplantation.

Figure 1. 'Rainy Day' Collections, Centre for Blood Cell Therapies, Peter MacCallum Cancer Centre, January 2001–December 2006.

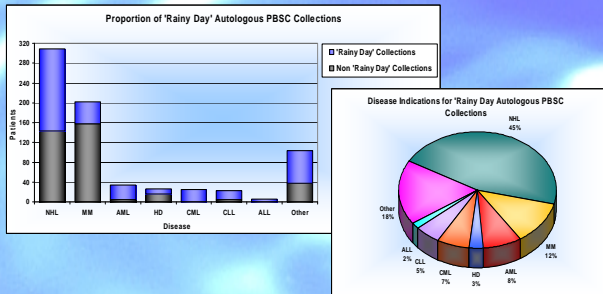


Figure 1. 'Rainy Day' Transplants, Centre for Blood Cell Therapies, Peter MacCallum Cancer Centre, January 2001–December 2006.

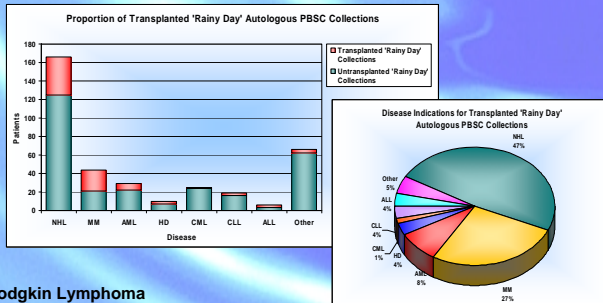
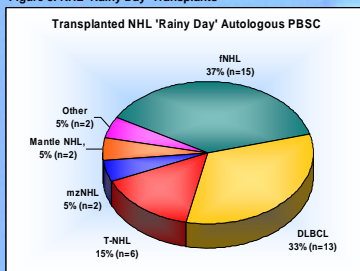


Figure 3. NHL 'Rainy Day' Transplants



Non-Hodgkin Lymphoma

- NHL has been the most common disease requiring Rainy Day APBSC collection and has resulted in 41 transplants, accounting for 24% of NHL Rainy Day collections and 47% of all Rainy Day transplants.
- The average time between collection and infusion for NHL transplants has been 1.74 years (SD = 1.60).
- Follicular NHL (fNHL) has accounted for the majority (37%, n=15/41) of NHL Rainy Day transplants, with 5 of 15 patients showing transformation of their fNHL into Diffuse Large B-Cell Lymphoma (DLBCL) (Refer to Figure 3).
- DLBCL has accounted for 33% of NHL Rainy Day transplants, 13 patients requiring eventual transplantation.
- The average time between collection and infusion for fNHL and DLBCL has been 2.07 (SD=2.01) and 1.84 (SD=1.62) years, respectively.
- Peripheral T-Cell Lymphoma (T-NHL) has contributed to 15% (n=6/41) of the transplanted NHL Rainy Day collections. Average time between collection and infusion has been 1.53 years (SD=0.97) possibly reflecting the fulminant cytological transformation observed in T-NHL.¹

Multiple Myeloma

- Despite the low incidence of Rainy Day collection, MM has shown to have the highest transplant turnover with 55% (n=23/44) of Rainy Day collections resulting in transplantation.
- The average time between collection and infusion has been 2.79 years (SD=1.65)

Acute Myeloid Leukemia

- Of 29 AML patients collected for Rainy Day APBSC collections, 7 (24%) have resulted in transplantation reflecting the fact that with post remission therapy, up to 30% of AML patients can remain in remission at 5 years.²
- The average time between collection and infusion of AML patients has been 1.61 years (SD=2.02)

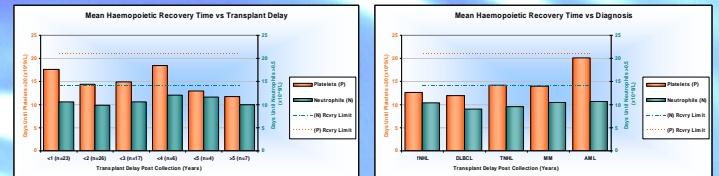
Chronic Myeloid Leukemia

- From January 2001 until December 2006, 25 patients with CML have had APBSCs collected, all of whom were collected on a 'Rainy Day' proviso.
- To date, 1 of these 25 patients has resulted in transplantation, 10 months following initial mobilisation.
- This low transplant turnover is not surprising given that current treatment regimens for CML can produce complete haematological responses in over 95% of patients, 74% of these achieving a major cytogenetic response.²

Haemopoietic Recovery of 'Rainy Day' Autologous PBSC

- The 84 patients transplanted within the 6 years following Rainy Day collection resulted in haemopoietic recovery within the specified limits. Recovery limits were set at 21 days for Platelets (P^0) and 14 days for Neutrophils (N^0).
- No evident relationship between transplant delay and haemopoietic recovery over time, suggesting that prolonged storage does not adversely affect engraftment. (Figure 4)
- Diagnosis resulted in little effect on haemopoietic recovery outcome (Figure 5).
- All major diagnoses resulted in engraftment within the specified recovery limit.
- Interestingly, AML patients demonstrated a slightly longer platelet recovery time, although still within the recovery limit.

Figures 4. & 5. Haemopoietic Recovery in 'Rainy Day' Transplants, Centre for Blood Cell Therapies, January 2001 – December 2006.



Subsequent Autologous PBSC Transplantation in Multiple Myeloma.

Conventional-dose chemotherapy followed by high dose chemotherapy with APBSC transplantation has been shown to be an effective first line treatment in patients with Multiple Myeloma (MM). Patients who experience relapse, increased myeloma burden or who have become refractory to first-line conventional-dose chemotherapy may require subsequent APBSC transplantation.³

- From January 2001 to December 2006, 14 patients of 158 with MM (13%) have had subsequent transplantation with APBSCs, collected during consolidation treatment as part of first line treatment with high dose chemotherapy.
- The median time between first and second infusions has been 1.88 years (SD = 0.95).
- For the 12 patients who achieved hemopoietic recovery following the second infusion, there is no significant disparity in the days until neutrophil and platelet recovery between the first and second infusions (days until $N^0 > 0.5 \times 10^9/L = 10$, $P^0 > 20 \times 10^9/L = 9$ and days until $N^0 > 0.5 \times 10^9/L = 10$, $P^0 > 20 \times 10^9/L = 11$ respectively) further indicating that storage period does not adversely affect the haemopoietic recovery potential of the cells.

Privatised Storage of PBSC's

Restricted storage capacity is often a limiting factor as far as 'Rainy Day' APBSC collections are concerned. In May 2004, the Peter MacCallum Cancer Centre undertook an initiative to offer a cohort of patients the opportunity to have their cells stored privately through a TGA licensed third-party off-site storage provider. The primary indications for this paradigm have largely been indolent disease, namely follicular lymphoma in a state of minimal residual disease (MRD), smoldering myeloma and CML with MRD post imatinib therapy.

- Since May 2004, APBSCs for 65 patients have been successfully transferred to an off-site storage location.
- The 65 patients constitute 68 mobilisations, accounting for 17% of all collections and 35% of 'Rainy Day' collections in the given time.
- Even in this low-risk cohort, to date, 3 out of 65 patients (5%) have required APBSC transplantation. All three patients suffered transformation of their primary NHL (2 fNHL, 1 mznHL) to DLBCL.
- Considering the latency of these diseases, and the often aggressive, chemotherapy-refractory nature of relapse, we expect these numbers to dramatically increase over time.⁴

Conclusion

Over a 6 year period (January 2001-December 2006) we collected Rainy Day APBSCs for 365 patients. To date, over 23% of these collections have eventuated in transplantation. We conclude that it is feasible and safe to perform 'Rainy Day' collections, although more stringent criteria would result in more efficient use of this resource intensive strategy.

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