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DEVELOPING A PEDIATRIC OUTPATIENT TRANSPLANTATION PROGRAM. THE CHILDREN'S MEMORIAL HOSPITAL EXPERIENCE

Lydia Gonzalez–Ryan,[1] Paul R Haut,[2] Kelly Coyne,[1] Karen Van Syckle,[1] Reggie Duerst,[2] Diana Haro,[3] Morris Kletzel[2]

[1] Children's Memorial Hospital, Stem Cell Transplant Program at Children's Memorial Hospital, [2] Division of Pediatric Hematology Oncology, Northwestern University, Stem Cell Transplant Program at Children's Memorial Hospital, [3] Northwestern Affiliated Transplant Centers (NUATC), Stem Cell Transplant Program at Children's Memorial Hospital

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1. ABSTRACT

We describe the development of a pediatric outpatient transplant program and our initial experience with autologous and allogeneic transplants performed partially or completely in the outpatient setting. Forty-eight autologous and seven allogeneic transplants have been performed in our institution in the outpatient setting between June 1994 and July 2000. The ablation used for the autologous outpatient transplants was VP-16 1000 mg/m^2/ day as a continuous infusion for 2 days and Carboplatinum 667mg/m^2/day for 2 days. The autologous inpatient transplants received Thio-tepa 300-mg/ m^{2}per day x 3 days and cyclophosphamide 60 mg/kg/day for 4 days. For those patients who received an immune-ablative allogeneic outpatient transplant, the regimen consisted of Fludarabine 30 mg/m^2/day for 6 days, followed by busulfan for children less than five years of age 1 mg/kg/dose x 8 doses and for those five years and older 0.8 mg/kg/dose x 8 doses, followed by ATG 40mg/kg/day x 4 days. Engraftment was complete in all transplants achieving an ANC >500 for the outpatient transplant in 15 days (10-35) vs. the inpatient in 15 days (14-58). This was not statistically significant. They achieved un-sustained platelets >20.0 by day 19 (14-58) for the outpatients and day 32 10-64) for the inpatient. The allogeneic immune ablative transplants were considered engrafted when their VNTRs were greater that 30% which was achieved at a median of 13 days (10-27). The economic data showed a statistically significant decrease in charges and direct costs between the outpatient (median charges $30 775, direct costs $8 389) and the inpatient (median charges $99 838, direct costs $42 757) transplants (p0.001). There was no difference in morbidity and mortality between the two groups but the use of empiric amphotericin B was markedly decreased in the outpatient transplants. In conclusion it is feasible and less costly to perform autologous hematopoietic stem cell transplants in the outpatient setting with no increase in morbidity and mortality. For the allogeneic transplants there is not yet enough data to establish a similar conclusion.

2. INTRODUCTION

Advances in the field of stem cell transplantation have lead to innovations in the treatment of children with malignant and non-malignant diseases making use of this technology. The use of Peripheral Blood Stem Cells (PBSC) in the autologous, as well as in the allogeneic setting, and the use of immuno-ablative ("mini" transplants) conditioning regimens have lent themselves to be performed in the outpatient setting (1, 2). The concept of outpatient transplantation is attractive for several reasons including the potential for decreased cost and improved quality of life for the patient during the treatment. We have taken the approach of dividing outpatient transplantation into partial, where some aspects of the transplant are done in the outpatient setting (i.e. TBI or the post transplant care is provided in the ambulatory setting) and complete where all care is delivered in the outpatient setting (3, 4). To date

Table 1. Regimens utilized in pediatric outpatient transplantation.

Type of Transplant	Drugs	Doses	Days
Outpatient autologous	Etoposide (VP-16)	1000mg/m^2/day as a continuous infusion.	–3,-2
	Carboplatinum	667 mg/m^2/day	–3,-2
Inpatient autologous	Thio-Tepa	300mg/m^2/day	–6.-5,-4
	Cyclophospahmide	60mg/Kg/day	–4.-3,-2,-1
Allogeneic immuno-ablative outpatient.	Fludarabine	30 mg/m^2/day	–10,-9,-8,-7,-6
	I.V Busulfan	< 5 years of age 1mg/kg/dose x 8 doses. >5 years of age .8 mg/kg/dose x 8 doses	–5,-4
	Anti-thymocyte Globulin (ATG)	40mg/kg/day	–4,-3,-2,-1.

Table 2. Outpatient Hematopoietic Stem Cell Transplant care.

Procedure	Partial	Complete
Peripheral Stem, Cell Harvesting	X	X
Administration of TBI	X	X
Administration of conditioning chemotherapy	+/-	X
Infusion of Stem Cells	X	X
Pre- engraftment assessment and management		X
Post-engraftment assessment and management	X	X
Infusional Services	X	X
Blood product support	X	X
Fluid and electrolyte support	X	X
I.V. antibiotics	X	X
Pain Management		X
Fever and neutropenia management		
Hemodinamically stable	X	X
Hemodinamically un-stable		

this practice has been primarily used by adult centers with autologous transplantation (5, 6). This approach has been undertaken with less enthusiasm by pediatric centers mainly because of concerns about infection, safety, limited isolation, patient and family compliance, and the lack of adequate resources both of personnel and facilities. In this review we will present the experience of Hematopoietic Stem Cell Transplantation (HSCT) in the ambulatory setting at Children's Memorial Hospital (CMH) between 1995 and 2000. We will outline the process undertaken and the results of our experience.

3. MATERIALS AND METHODS

3.1. Patients

Between June 1994 and July 2000, seven allogeneic and 48 autologous HSCT were performed in the outpatient setting at CMH. Patients were enrolled in one of three protocols outlined in Table 1. These protocols were for the treatment of children with high risk neuroblastoma using a triple tandem autologous PBSC rescue and Immune-ablative HSCT for malignant and non-malignant diseases utilizing allogeneic PBSC (see Table 1). Twenty-two patients with newly diagnosed stage 4 neuroblastoma over the age of 1 year, one patient with stage three MYCN amplified and one patient with recurrent stage 2 disease with *MYCN* amplification were enrolled on the autologous transplant protocol. Three other patients were treated according to this protocol but where not enrolled on the study. This protocol called for the first two of three PBSC rescues to be performed in the outpatient setting and the final to be performed as an inpatient. Seven children received their allogeneic stem cell transplant using the immuno-ablative protocol including: one patient with Thalassemia, two patients with Hyper-IgM syndrome, one patient with Sickle Cell Anemia, and two patients with acute leukemia. One patient with SCID syndrome who did not receive ablation also received his transplant in the outpatient setting.

3.1.1. Patient and family selection criteria

Patient selection for participation in the outpatient program included: a careful social and economic history to assess ability of the family to carry out the tasks required from them:

1. Identification of the caregivers, with emphasis on their abilities to be trained for the tasks.

2. Determination of adequacy of either the patient's home or a transitional home geographically closes to our institution.

3. Assessment of transportation needs and communication.

4. Approvals by the patient's insurance carrier to provide appropriate home health care.

5. Willingness of the family to participate in the program.

3.1.2. Ambulatory Stem Cell Transplant Unit (ASCU)

All patients were nursed in a 5 bed ASCU located on the 4th floor of CMH, outside the inpatient facility. The unit is equipped with a HEPA filter air handling system and each room has enhanced monitoring technology of blood pressure, ECG, respiratory rate and pulse oximetry. Each room is equipped with TV, VCR and Internet access for patient and family entertainment. Three FTE transplant trained clinical nurses and one pediatric nurse practitioner staff the unit, with a clerical person. The unit is open weekdays from 8:00 a.m. to 8:00 p.m. The unit is equipped with two pheresis machines (COBE Spectra) to perform peripheral blood stem cell collections.

3.1.3. Indications for admission to the inpatient unit

Patients were admitted to the inpatient unit if they met any of the following criteria: 1) fever and neutropenia, with or without hemodynamic stability, 2) Severe pain requiring the administration of narcotics, 3) Other significant illness without fever (i.e. seizures, pancreatitis etc.), 4) social reasons (Table 2)

3.1.4. Economic Data

The economic data collected include hospital and physician charges for the first 30 days as well as the cost of home health care for the outpatient transplants during the

Table 3. Comparison between outpatient and inpatient transplants in patients enrolled on the Chicago Pilot #2

Parameters	Inpatient (n=23)	Outpatient (n=48)	P value
LOS (days)	16.1 (11-29)	7.1 (2-65)	0.001
Bacterial isolates	11/23	5/48	0.001
Fungal isolates	2/23	2/48	n.s.
Empiric amphotericin B (days)	6.5 (2-27)	0	0.0001
100 day mortality	1/23	0/48	n.s.
ANC >500	15 (14-58)	15 (10-35)	n.s
Plat >20.0	32 (10-64)	19 (14-58)	0.01

Table 4. Economic comparison between autologous Stem Cell Transplants in the inpatient vs outpatient.

site	Charges Median (range)	Direct Costs Median (range)	P value
Inpatient	$99 835 ($84 000 -$179 000)	$25 757 ($22 000 – $48 000)	0.001
outpatient	$30 775 ($20 000 - $38 000)	$$8 389 ($5 000 - $11 000)	0.001

same 30 days. A break down of the charges by area is not available, only as a total of charges and direct costs for that period of time.

4. RESULTS

4.1. Autologous PBSC Rescue

A total of 27 patients were treated per the Chicago Pilot #2. Forty-eight of the anticipated 54 outpatient rescues were actually performed in the outpatient setting. Three patients only received one of their 3 planned PBSC rescues, one and due to an aspergillosis infection, one due to persistent vomiting and one due to parental refusal. The median LOS for this group of patients was 7.1 days with a range from (2-65). The reasons for admission in this group included fever and neutropenia (n = 35). In 10 episodes positive blood cultures were found and three patients developed aspergillosis. In the remaining episodes no source of infection was detected. One patient was admitted with pneumonia caused by adenovirus and subsequently developed an aspergillus infection in the lung (LOS 65 days). There were no toxic deaths. For the outpatient PBSC rescues the median time to an ANC >500 was 15 days (range of 10 to 35) and to a platelet count >20.0 was 19 days (range of 14 to 58). Twenty-two patients proceeded to the 3rd inpatient PBSC rescue. The median LOS was 16.1 days (range of 11-29) $p<0.001$. The median time to engraftment for this group of patients was 15 days to an ANC >500 (range of 10 to 22) and 32 days to a platelet count >20.0 (range of 10 to 64). From the entire cohort of patients 20 patients remain free of disease with a median follow up of 42.5 months (range 9 to 64 months). (Table 3).

All 7 allogeneic HSCT were performed in the outpatient setting. Five of the patients received cells from matched related donors and 2 received matched unrelated stem cells. The median length of stay for this group was 4.2 days (range of 2-32). The reasons for admission were fever and neutropenia in 5/7 patients, viral meningitis, and one episode of failure to engraft and sepsis. One patient had three admissions for evaluation of seizures due to scheduling and insurance issues. Engraftment was assessed by VNTR's and sex determination in this group. Engraftment was defined as >30% donor origin DNA and was detected by a median of 13 days (range of 10-27). One patient received a boost of stem cells to improve engraftment.

Economic results are shown in Table 4. For purposes of cost comparison the median total hospital charges for the autologous PBSC rescues performed as an outpatient were compared to those performed as an inpatient for the patients treated per the Chicago Pilot II. For the data we compared 38 transplants performed in the outpatient setting with 27 in the inpatient facility. The outpatient charges were a median of $30,775.00 (range $20,000 to $38,000), while the median inpatient charges were $99,838.00 (range $84,000 to $179,000) p=0.001. The direct costs for the outpatient transplants were $8 389.00 (range $5,000 to $ 11,000), while for the inpatient transplants the direct costs were $25,757.00 (range $ 22,000 to $ 48,000) p= 0.001.

5. DISCUSSION

Despite concerns regarding the safety of outpatient transplant management in pediatrics, the emphasis in healthcare cost containment continues to shift complex stem cell transplant care from the inpatient to the outpatient setting (7, 8). Tied to economic changes are the new therapeutic directions in stem cell transplantation like the use of PBSC in transplantation that allows faster engraftment, the use of "mini' transplants which limit toxicities, and donor lymphocyte infusions. The success of pediatric transplantation is driven in part by both scientific advances and economic pressures to reduce cost. This requires the establishment of the appropriate infrastructure to support the management of acute ambulatory care. It is essential to create an integrated program that includes an ambulatory clinical facility, a pheresis center, transitional housing and a dedicated home health agency that is willing to partner with the transplant center.

Another important component governing an outpatient strategy is the establishment of standards of care and clinical algorithms that are applicable to this setting. This requires the development of stringent selection criteria and reliable systems of communication and accountability. Integration of essential services ensures positioning of the program to be able negotiate global rates that are applicable and flexible to this new reality (9, 10, 11).

One of the greatest obstacles is determining the actual cost of an outpatient transplant. This has added importance since resource allocation and utilization, depend on this often difficult to obtain data (12). Lastly outcomes monitoring and analysis are critical not only to

document clinical success and quality, but also to provide financial data to the transplant center and to payors (13, 14, 15). Our program was developed by reacting to needs rather than prospectively developing the needed systems. We started performing outpatient transplantation before the infrastructure was in place, and for that simple reason the collection of data and the resource utilization was overestimated in some areas and underestimated in others.

The concept of outpatient transplant is broader than simply the delivery of care in an outpatient setting. Instead it implies a complete approach to the care of stem cell transplant patients which supersedes previous paradigms for care. In our experience with the limitations that we had, we have divided the outpatient concept into a partial or complete (see Table 2) and we have developed the protocols to utilize our present infrastructure. What we mean by a partial transplant is that portions of the procedure are done in the ambulatory setting such as outpatient TBI, early discharge, ablative chemotherapy, stem cell harvest, etc. The main purpose of this approach is to reduce inpatient hospital days and shift the high cost of inpatient care to a less expensive setting. Not all patients or protocols are amenable to this setting.

Providing care to the pediatric transplant patient requires access to a dedicated facility and appropriately trained staff resources. Facility planning becomes paramount, regardless of whether the space is newly created or simply being prepared to accommodate the outpatient transplant program. The layout and flow can greatly impact infectious risks, emergency access to patients and patient/family satisfaction. The space necessary to accommodate an outpatient pediatric transplant will be based primarily on the clinical approach taken by the transplant team. In our program we started with the use of a day hospital shared with Hematology and Oncology. It rapidly became clear that that facility was inadequate care of an outpatient transplant population, primarily due to a lack of isolation rooms and proper ventilation. At this point we embarked in the planning of a unit dedicated exclusively to transplant patients but also flexible enough to accommodate the overflow of the day hospital. Because of space limitations in our institution we were limited to a 5-bed outpatient HEPA-filtered transplant facility. Four out of the five rooms are designed as acute care infusion rooms with capability of monitoring B/P, pulse, EKG, pulse oximetry and also have the proper equipment for emergent care. The 5th room was designed as a clinic room to assess patients prior to transplant or patients whose only need was to have a physical exam or blood drawn. The four larger rooms are also equipped to perform dialysis and pheresis.

Access to a transitional housing facility can also impact on space requirements. A well-planned transitional housing facility can facilitate the administration of uncomplicated infusion care, monitoring of laboratory test and ongoing physical assessment by home health care personnel. In many centers transitional housing and home care partnerships go hand in hand to provide daily care outside the hospital (16, 17).

Home health support affords the transplant team the opportunity to enhance patient/family satisfaction while delivering quality cost-effective patient care (18). We believe that a working relationship between the transplant team and the home care team can successfully promote continuity of care, enhance physical assessment and patient monitoring, minimize complications and positively affect patient outcomes. A successful transplant program/home care provider partnership should not imply a shared financial and contractual relationship but rather a relationship based on shared commitment, mutual benefit, and demonstrate quality and value with the ultimate goal being patient optimal care and satisfaction. It is essential that both parties collaborate to develop specific guidelines for patient care, patient and staff education, therapy delivery and communication. The partnership should be able to accurately measure and monitor clinical and economic outcomes. A primary home care provider is best, but is neither always realistic nor competitive. In the environment of managed care restricted referrals, it is prudent to develop several relationships with home care programs. The transplant associated home health care cannot be traditional home care, limited to infusion care, lab draws and nursing assessment. The level of care provided must be at a higher level with pediatric and oncology backbones, paralleling the care administered to a patient in the hospital facility (19).

When we look at the results obtained from this approach, one can conclude that it is safe to performed outpatient transplantation in pediatric patients. The morbidity and mortality are no different than that observed in the in-patient setting, with the exception of a decrease in outpatient use of empiric amphotericin B and a decrease in fungal infections overall. The economic data presented reflects charges and direct cost for the first 30 days post-transplant and one can immediately see the cost savings that outpatient transplantation generates. It is also important to understand that this approach is not feasible without proper contracting.

In summary the development of an outpatient transplant program requires careful planning, appropriate facilities and trained personnel, and above all a commitment to a new approach to care of pediatric stem cell transplant patients. It demands flexibility to accommodate the rapidly changing field and the economic pressures. This necessitates an evolving process rather than a fixed program. Based on our experience we can conclude that outpatient transplantation in pediatrics is feasible, economically sound, and above all safe for the patient.

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Send correspondence to: Morris Kletzel, M.D., Division of Pediatric Hematology Oncology, Children's Memorial Hospital box #30, 2300 Children's Plaza, Chicago IL 60614, Tel: 773-880-3265, Fax: 773-880-3019, E-mail: mkletzel@northwestern.edu