RESEARCH PAPER

HOSPITAL IN THE HOME (HITH) CARE FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION FOR LYMPHOMA AND MULTIPLE MYELOMA.

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ABSTRACT

Background:

Advances in outpatient and supportive care and increased pressure on hospital bed usage has led to the investigation of hospital in the home (HITH) management following autologous haematologous stem cell transplantation (AutoHSCT) for patients with multiple myeloma or lymphoma.

Design:

The Newcastle Mater Hospital Haematology Unit together with the Mater Acute Care Community Service (MACCS) developed a protocol for HITH care following AutoHSCT.

Outcomes:

Clinical outcomes of the protocol were audited: 40% (13) of patients were suitable candidates for HITH care post transplantation. Of these 84.6% (11) were readmitted to the haematology unit within seven days of discharge from hospital.

Conclusion:

Our preliminary experience suggests that with adequate infrastructure support and rigorous patient selection this model of care is both safe and feasible.

BACKGROUND

Recent advances in health care delivery have allowed the treatment of patients at home who would otherwise have previously been treated in hospital. Hospital in the home (HITH) refers to the delivery of acute hospital care to patients at home. HITH may either substitute for the entire in-hospital admission (pure HITH) or a part of the hospital admission (mixed HITH). In Australia, HITH covers a diverse range of conditions, programs, providers and funding arrangements (Ruth et al 2001).

LITERATURE REVIEW

Data regarding outcomes of HITH are contradictory. A number of studies, including some randomised controlled studies, have shown that HITH is safe; that patient outcomes in many conditions are equivalent for patients using HITH and in-hospital care (IHC); and that both perceived quality of life and patient satisfaction are greater with HITH than with IHC (Davies et al 2000; Caplan et al 1999; Montalto 1998; Donald et al 1995; Cummings et al 1990). Two systematic reviews of HITH have been performed and each found no significant difference in health outcomes between HITH and IHC (Shepperd and Iliffe 2000; Soderstrom et al 1999). In part, these results reflect the fact that HITH has been applied to a wide range of conditions and therapies, and that outcomes of HITH may vary as a result.

In recent years, developments in chemotherapeutics and supportive care have made outpatient care of a number of haematological malignancies a possibility. Outpatient management has been shown to be a safe,

well-accepted and cost-efficient option in the treatment of a number of conditions including: febrile neutropenia related to chemotherapy, acute promyelocytic leukaemia and acute myeloid leukaemia. (Paganini et al 2003; Allen et al 2001; Johansson et al 2001; Aquino et al 2000; Girmenia et al 1999; Ruiz-Arguelles et al 1999; Lowenthal et al 1996).

Developments in therapeutics and supportive care have also made HITH care for varying types of haematopoietic transplantation a possibility. Autologous stem cell transplants, reduced-intensity allografts and conventionally conditioned allografts have all been successfully performed on an outpatient basis. The majority of experience has been with granulocyte-colony stimulating factor (G-CSF) supported autologous bone marrow or peripheral blood stem cell (PBSC) transplantation. Results from published studies suggest that outpatient autologous haematopoietic stem cell transplantation (HSCT) can be performed safely for patients with metastatic breast cancer and multiple myeloma, with reduced length of stay and hospital charges, without evidence of increased clinical complications or out-of-pocket expenses to patients (Rizzo et al 1999; Meisenberg 1997; Peters et al 1994; Sullivan et al 1994).

There are smaller numbers of reports of allogeneic HSCT being performed on an outpatient basis, although both myeloablative and non-myeloablative, reduced-intensity transplants have been performed in the ambulatory setting. The development of non-myeloablative conditioning protocols, in particular, has made routine outpatient HSCT a distinct possibility.

A number of studies have demonstrated that non-myeloablative allogeneic transplantation using both immunosuppressive, fludarabine-based conditioning regimens, and radiotherapy-based conditioning regimens is feasible and is not associated with a higher treatment related mortality (TRM) or a higher rate of long-term complications. It is acceptable to patients and their families, is less emotionally distressing for caregivers of HSCT recipients, is more able to meet their needs, and is achievable in the majority of patients (Ruiz-Arguelles 2001; Grimm et al 2000; Ruiz-Argelles 2000; Algara 1994). Furthermore small studies of HITH following conventional allografting has suggested that it may be associated with several advantages including: faster discharge; reduced need for total parental nutrition (TPN); a lower incidence of acute graft versus host disease (GvHD); lower TRM; and lower costs, although these findings require confirmation in large prospective randomized studies (Svahn et al 2002).

Of the published studies of HITH following autologous transplantation, the majority report experience from the United States of America. There are no published reports of HITH care for transplantation in an Australian setting. In this paper we report feasibility data from an audit of an Australian haematology unit's experience of partial episode substitution (mixed HITH) following high-dose chemotherapy and autologous stem cell transplantation for patients with Hodgkin's lymphoma, non-Hodgkin's lymphoma and multiple myeloma.

METHOD

For the purpose of reviewing the protocol development of HITH care following AutoHSCT we undertook an audit of our clinical outcomes.

Patient eligibility for Hospital-in-the-home (HITH) care

Patients undergoing autologous HSCT are referred to the HITH service by the haematology team.

To be eligible for consideration for HITH care patients must be undergoing autologous HSCT following either LACE (Lomustine, Cytosine Arabinoside, Cyclophosphamide and Etoposide) or melphalan conditioning, give informed consent, be over 18 years of age, medically stable, have available appropriate carer supervision, have a suitable home environment; be able to use their own toilet and administer their own oral medication, have access to a home telephone and available transport and be compliant with therapy. Patients would not be considered suitable for HITH care if they are: unable to comply with these conditions, are geographically isolated (live more than 45 minutes by road from hospital), unable to understand or comply with treatment or require therapy more than once per day.

Transplant conditioning

Patients with Hodgkin's Lymphoma and non-Hodgkin's Lymphoma received transplant conditioning with the LACE regimen. LACE consists of Lomustine 200mg/m^2 orally on day 7, Etoposide 1000mg/m^2 on day 7, cytosine arabinoside 2g/m^2 on days 6 and 5 and Cyclophosphamide 1.8g/m^2 on days 4 to 2 inclusive.

Patients with multiple myeloma (MM) were conditioned with melphalan 200mg/m^2 given intravenously over 1 hour on day 2.

Supportive care

Blood samples were collected daily for full blood count (FBC) and biochemistry.

Red cell transfusions were given if the patient had a haemoglobin (Hb) level less than 80g/L and platelet transfusions when the platelet count fell below 10 x 109/L or if there were signs of haemorrhage. All blood products were irradiated.

All patients received mouth care and infective prophylaxis with norfloxacin 400mg orally bd, aciclovir 400mg orally tds, fluconazole 200mg orally bd, chlorhexidine mouthwash 10mls qid and nystatin oral solution 1ml qid.

Granulocyte colony-stimulating factor (G-CSF) at 5mcg/kg per day was administered from day one after stem cell transplantation until the Absolute Neutrophil

Count (ANC) was greater than 0.5 x 109/L for two consecutive days.

Veno-occlusive disease prophylaxis was with enoxaparin 40mg SC daily.

Mucosal pain was initially treated with oral paracetamol and oral morphine. If this was insufficient continuous intravenous morphine was administered using a pump.

Post-transplant HITH care

All patients suitable for HITH care were provided with an outpatient management plan prior to discharge with details of the care to be provided by the HITH team and indications for contacting the HITH nurse or attending the haematology day ward or the emergency department.

HITH nurses attend patients daily to assess their progress and administer therapy. Therapies commonly administered by HITH staff include intravenous antibiotics and subcutaneous injections such as G-CSF and/or enoxaparin. At each daily visit the HITH nurse performs a structured clinical assessment which records details of a relevant history and examination including: assessment of symptoms, temperature, pulse, blood pressure, central venous access, oral mucosa, skin integrity, oral intake, fluid balance, urine output and weight. All toxicity grading is performed according to World Health Organisation (WHO) guidelines with the results recorded on a post-transplant flow sheet.

Post-transplant investigations (daily FBC, biochemistry and urinalysis) are also attended by the HITH nursing staff. The results of these routine investigations are then reviewed by HITH nurses, who may then arrange outpatient transfusion of red cells or platelets as necessary. Any clinical concerns that the HITH care nurse has are discussed with the attending haematologist, who may choose to review the patient as an outpatient as necessary. Clinical problems arising after working hours are addressed by the medical registrar on-call and by the attending haematologist. HITH patients requiring admission for inpatient care are admitted to the haematology ward under the care of the attending haematologist.

OUTCOME MEASURES

For the purpose of this audit descriptive data were collected on age and gender, diagnosis, transplant conditioning, inpatient length of stay (pre-discharge and post-readmission), and duration of HITH care. Details of a series of outcome measures that may be used as de-facto indicators of the safety and feasibility of HITH care were collected. These included patient-initiated telephone calls, unscheduled staff call-outs, incidence of unplanned readmission to hospital, reasons for readmission, morbidity and toxicity (according to WHO criteria), mortality (during admission and transplant-related mortality at day 100), incidence of infection, antibiotic use, incidence and severity of mucositis, incidence of renal failure, bleeding incidence and severity (according to WHO criteria) and transfusion requirements.

RESULTS

Patient characteristics

Between March 2001 and June 2003, 33 patients underwent autologous HSCT for lymphoma or multiple myeloma at the Hunter Haematology Unit. Of these, 16 were judged to be suitable candidates for HITH care post-transplant and were offered the option. Unfortunately, after consenting to HITH care three patients subsequently developed medical complications necessitating inpatient care for the duration of the treatment episode. The data presented is on the 13 transplant recipients who received HITH care following autologous HSCT. Of these candidates 10 were males and three were females, giving a 10:3 ratio of males to females. The average age was 48 years (sd14.83). For the transplant recipients not offered HITH care, this decision was made on the following grounds, six patients lived outside the agreed geographical area, six were medically unstable, three lived alone, one patient was assessed to be non-compliant with therapy and one patient was excluded due to an unsuitable home environment.

From the 13 patients treated under the HITH program, nine received a LACE-conditioned transplant for lymphoma and four received a melphalan-only conditioned transplant for myeloma. Patients with lymphoma can be further classified as two with diffuse large cell non-Hodgkins lymphoma (NHL), two with follicular NHL, three with Hodgkins lymphoma; and two with a diagnosis of other forms of NHL (unclassified and small cell).

Table 1: Patient demographics

Age	M/F	Diagnosis	Chemotherapy regime	Readmission required Y/N
52	M	HD	LACE	N
59	M	NHL	LACE	N
50	M	NHL	LACE	Y
32	M	Lymphoma	LACE	Y
55	M	NHL	LACE	Y
20	M	HD	LACE	Y
59	M	NHL	LACE	Y
22	F	HD	LACE	Y
62	M	NHL	LACE	Y
66	M	Myeloma	Melphalan	Y
51	M	Myeloma	Melphalan	Y
54	F	Myeloma	Melphalan	Y
41	F	Myeloma	Melphalan	Y

Stem cell inoculum

Of the 13 patients who underwent autologous HSCT for multiple myeloma or lymphoma, the mean stem cell inoculum was 8.3 x 106/kg (range 1.8-20.2 x 106/kg).

Engraftment

Patients that underwent LACE conditioning achieved neutrophil engraftment (0.5x109/L) by day +10 (range day 9-12) and platelet engraftment (unsupported platelet count > 50 x 109/L) by day +24 (range 13-35). Patients conditioned with melphalan generally achieved neutrophil engraftment by day +11 (range day +10-13) and platelet engraftment by day +20 (range 15-25).

G-CSF use and transfusion support

Patients undergoing LACE conditioning received an average of 11 daily doses of G-CSF (range 9-14 doses), whereas patients receiving melphalan conditioning received an average of 12 doses of G-CSF (range 10-13 doses).

The majority of transplant recipients did not require significant blood product support. LACE-conditioned transplant recipients required an average of 3 units of packed cells (range 1-9) and 18 units of platelets (range 8-32) while melphalan conditioned transplant recipients required 3 units of packed cells (range 2-4) and 9 units of platelets (range 4-12).

Transplant-related Toxicity

Autologous HSCT with either LACE or melphalan conditioning was generally well tolerated. The major toxicity of transplantation was febrile neutropenia, which accounted for the majority of readmissions but did not result in the death of any transplant recipients. No patients required intensive care admission. Of those patients who underwent a LACE autograft, six patients experienced grade 1 to grade 3 mucositis (mean grade 1), while all four patients who underwent a melphalan autograft experienced greater than grade 2 mucositis (mean grade 3). Of all the patients who underwent HITH care, only five experienced any bleeding complications, and in all cases this was mild (grade 1). Only one patient developed renal dysfunction with a transitory rise in the serum creatinine greater than 120ummol/L.

There were no deaths in the HITH cohort. All 13 patients managed at home on the HITH program were alive on day +100 post-transplant with none demonstrating evidence of disease progression.

Discharges from hospital

Two patients (15%) were discharged from hospital for HITH care on the day of transplant; seven (53%) were discharged on day +1 post-transplant; one (7.6%) on day +2 and three (23%) left hospital on or after day +3.

Readmissions following HITH care

Eleven of the patients (84.6%) managed on the HITH program required readmission to the haematology unit within 7 days of discharge from hospital. Febrile neutropenia / sepsis accounted for 81.8% (n=9) of these readmissions. Four of these patients did not have a pathogen identified though two presented with symptoms of severe mucositis. No evidence of line infections or other specified sources were confirmed though blood cultures were positive in five cases. Two patients had blood cultures positive for strep viridens, one for E coli, one for staph aureas, and one for a coagulase negative staphylococcus. The readmission length of stay ranged from 5 to 12 days (mean 8.5) and all patients were discharged to their own homes at that time.

Of the remaining two patients requiring readmission to hospital: one patient was admitted for treatment of a venous thrombosis and one for management of severe (grade 4) mucositis. All patients discharged for HITH care on or after day +3 post-transplant required readmission, suggesting that this group of patients may not have been appropriate candidates for HITH care.

DISCUSSION

HSCT is an intensive treatment modality with a 100 day treatment related mortality (TRM) of 1-50% depending on the type of transplant. In the past, the toxicity associated with HSCT has mandated inpatient care, with lengthy inpatient admissions. Developments in transplantation and supportive care have made outpatient care a possibility. The combination of antimicrobial prophylaxis, simplified pre-transplant conditioning and non-myeloablative regimens has made possible the performance of HSCT entirely on an outpatient basis. While only a small number of studies of outpatient HSCT have been done, the results of published studies suggest that outpatient HSCT can be achieved with equivalent efficacy as inpatient transplantation and without an increase in morbidity or mortality.

This report suggests that autologous transplantation using a HITH care delivery model is feasible and is safe for appropriately selected patients (40% of our patients) with lymphoma and multiple myeloma. Our results also suggest that there may be merit in exploring HITH models of post-transplant care as a means for increasing patient satisfaction with care and reducing the costs of care.

LIMITATIONS

There are a number of limitations to this report. We report only a small cohort of HITH care patients unmatched to IHC episodes and as such can make only limited conclusions regarding adverse events and mortality associated with HITH transplantation care. Patients were also not randomised between inpatient care and HITH care and indeed the rigorous selection criteria for HITH care mean that a selection bias is inevitable with younger, healthier, more compliant patients with less co-morbidity more likely to be offered outpatient care post-transplant. Finally, we also did not measure costs to families, carers or the community and as such are unable to explore the

degree of cost shifting that occurs with HITH transplantation.

Whether our (ongoing) experience has any relevance to other Australian transplant centres remains to be shown. Newcastle is a small city (population 470,610) and traffic congestion is mild compared with major metropolitan centres. Whether HITH transplantation care can be delivered successfully in other centres would require consideration of local factors, including transport infrastructure, hospital and transplant unit design and organisational structure of outpatient and home care services. Indeed, great care must be taken in extrapolating from studies of HITH care, such as ours, as there may be significant differences in conditions, in the model of HITH care, in the financial and structural organisation of health services and in the data gathered and reported by the researchers (Ioannides-Demos et al 2001, KPMG Consulting 1999).

The majority of participants in our HITH post-transplant program required readmission to hospital (n=11, 84.6%). In most instances this was because of the development of febrile neutropenia. Importantly, none of the patients experienced any clinical consequence as a result of this infection and all were subsequently discharged from hospital following engraftment. This is an important finding as unexpected return to hospital during HITH care can highlight difficulties with eligibility criteria, care choice, skill of assessor, and poor initial choice of therapy or misdiagnosis or can be an indicator of an effective monitoring system, whereby vigilant clinical supervision prevents an adverse negative outcome (Montalto et al 1999).

While our readmission rate is substantially higher than that reported in other studies, the absence of any major toxicity would suggest that our results may be explained by the absence of an outpatient care protocol for the management of febrile neutropenia and by a liberal readmission policy (Ruiz-Arguelles et al 1998; Jagannath et al 1997).

While HITH care following HSCT appears to be an attractive option, transfer of care to the outpatient setting is not without its problems.

Compliance of patients with medical treatment cannot be assured in the home with the same degree of certainty that it can in hospital and earlier hospital discharge following HSCT may be associated with a delay in resumption of oral energy intake and discontinuation of intravenous (IV) fluids (Stern et al 2000; Kane 1995). Research from outpatient HSCT programs in the United States of America has also found that loss of appetite, fatigue, continuous low-grade nausea and insomnia may frequently complicate outpatient care following transplantation, despite increased patient and caregiver satisfaction with outpatient care (Lawrence et al 1996). Indeed, evidence that outcomes may be no better, or even worse, than inpatient care has led some to express concern that the impetus for change to outpatient models of care has more to do with cost shifting than real concern for patient welfare.

Given the intensity of treatment, the presence of predictable neutropenia, the likelihood of adverse effects related to transplant conditioning and the site of care delivery, there will always be a predictable level of expected and unexpected intervention associated with HITH care for autologous HSCT. Enthusiasm for HITH care must therefore be tempered by recognition that HITH programs require a minimum level of infrastructure support including, effective incorporation of pathology services, 24-hour emergency care and telephone support, a rigorous system of monitoring and evaluation and a structured process for the return of HITH patients to hospital. Such programs also require the availability of nursing expertise for outpatient care, adequate communication between medical and nursing staff and between inpatient and outpatient services and the availability of an outpatient clinic able to provide medical assessment, transfusion services, intravenous infusions and facilitated admission where appropriate. It must also be stressed that outpatient care cannot be offered to all patients and that a careful selection process is critical. Only those who are compliant with therapy, able to attend outpatient follow-up, have a suitable home environment, have adequate support available 24 hours per day at home and have a reasonable educational level, are candidates for home care following transplantation.

Finally, as ambulatory / HITH care is a relatively new development in medical service delivery, it is vital that such programs be rigorously established and carefully monitored in order to maximise their benefits for patients and for government.

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