

Outpatient allogeneic hematopoietic stem-cell transplantation: a review

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Abstract: Hematopoietic stem-cell transplantation (HSCT) is usually performed in well-equipped units inside a hospital. The cost of this in-hospital transplant is usually very high; therefore, this procedure is more difficult to perform in low- and middle-income countries. Autologous outpatient HSCT is now a common procedure; however, outpatient allogeneic transplants are more complicated. Only a few centers in the world have incorporated outpatient HSCT. This transplant requires special adaptation, like a day hospital, careful selection of patients, oral medications, and the patient must live relatively close to the hospital. The results until now suggest that this outpatient transplant is factible and similar to inpatient HSCT. The objective was to review and describe the different methods and results following an outpatient allogeneic-HSCT strategy.

Keywords: allogeneic, outpatient, stem-cell transplantation

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Introduction

In most centers in the world, hematopoietic stem-cell transplantation (HSCT) is traditionally performed in an isolated room located in a stem-cell transplantation unit. Outpatient HSCT is emerging as an attractive and safe alternative to hospital-based care. Since 1993, we started an outpatient program for autologous HSCT, and nowadays, it is a procedure routinely performed in many centers worldwide. After gaining experience with autologous HSCT, we developed an outpatient allogeneic-HSCT program using reduced-intensity conditioning (RIC), and in 1998, reported the first four patients successfully allografted as outpatients.¹ Facing difficulties in hospitals in Mexico common to many low- and middle-income countries (LMICs), we have found that performing transplants outside the hospital setting is more affordable, safe, and endowed with similar results, representing a more realistic strategy to increase access to a potentially life-saving therapy which is unfortunately performed very little outside high-income countries (HICs).^{2,3} Currently, only a few HSCT centers

around the globe perform outpatient allo-HSCT.^{1,4–11} The objective of this review, is to describe different methods and results following an outpatient allo-HSCT strategy and provide experiences and advice in this setting for the transplanter.

Why do we perform outpatient transplants?

Outpatient transplantation eliminates the need for a sophisticated inpatient unit

Transplant units are a dedicated hospital area equipped with rooms designed to protect severely immunosuppressed patients with a combination of positive pressure, laminar airflow, and/or high-efficiency filters and independent water filtration systems. These units are staffed by specially trained nurses and physicians around the clock, often with restrictive patient visitation policies that prevent physical contact with their families and loved ones. Furthermore, hospital stays are usually 3–4 weeks long if no complications arise.¹² Consequently, these units are restricted to a few

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reference centers that have the resources to develop one, with access to transplantation limited by the number of hospital beds available at any given time.

More than 80% of the world's population lives in LMIC.¹³ HSCT programs in these countries face numerous problems stemming mainly from limited resources. Very few hospitals have HSCT units, and the existing units may not have laminar airflow or high-efficiency filters installed, problems that should not turn into obstacles to conduct HSCT.¹⁴ Thus, outpatient HSCT is a reasonable option for any country in the world but even more appealing for LMICs. Although transplants have increased in recent years in LMIC, there are still 20- to 40-fold fewer HSCTs compared to the United States and Europe.¹⁵ Still, there is no precise information in this setting, and we do not know the number of HSCT performed in LMIC.

By overcoming these problems in our country, we have conducted auto and allografts on an outpatient basis. We are convinced that this is a practical, if not the best option, for patients living in LMIC, where very frequently, the choice is between no-HSCT or an outpatient HSCT.¹⁴ Conducting both auto and allo-HSCTs on an outpatient basis have also resulted in our ability to perform grafts in special adverse circumstances such as those from the COVID-19 pandemic.^{6,16,17}

Outpatient transplants are more affordable and therefore more accessible

The median cost of an outpatient autograft in our experience ranges between 7500 and 10,000 USD,^{18,19} in addition to median-out-of-pocket expenses and 1-year follow-up costs, which have been reported at 1605 to 1640 USD, respectively.¹⁹ These costs are substantially lower than those reported from HSCT programs in HICs, where the median costs range from 100,000 to 150,000 USD. In this context, data suggest that the cost of outpatient autologous HSCT is approximately 50% of the cost of the in-hospital procedure in the same institution.²⁰ Outpatient allografting in our experience has a cost ranging from 12,000 to 18,000 USD.^{18,19,21} In India, outpatient HSCTs are similar with a median of 17,914 USD (range: 10,832–44,701).²² On the other hand, these figures in the United States and

other HIC range from 150,000 to 400,000 USD or even more.²³

Outpatient transplants are safe

Lessons learned in the field of outpatient autologous HSCT are several. The morbi-mortality seems to be lower than transplants conducted in hospitals; however, there is no formal comparison. Infections could be less frequent and severe than in inpatient programs, and the patients' quality of life is improved.^{24–26} The same has been described for allogeneic HSCT.²⁷ Moreover, it has been described that the long-term survival of patients allografted outside the hospital could be better, probably due to less-serious infections, different food quality intake, a lower prevalence of graft *versus* host disease, and a similar improvement in quality of life.^{28–30} Even though there is a logistic difference in HSCT performance, prognostic, and mortality indicators are similar despite the more limited resources and less-transplant experience.^{31,32} These data illustrate the growth of transplants in the last years in LMIC. Furthermore, the results of outpatient transplantation have shown variable results with overall survival (OS) ranging from 40% to 82%, a reported non-related mortality (NRM) from 8% to 35%, and a completely ambulatory transplant occurring in 21% to 100% (Table 1). In addition, lower drug costs have been reported in the outpatient setting.³²

How do we perform outpatient allo-HSCT?

Several patient characteristics are required, such as disease status, age, a good Karnofsky score, home address, support net, an adequate caregiver, and details of the transplant center and specifications of its program. Characteristics of diverse transplant centers around the world may differ regarding the type of transplant and conditioning, pre-transplant chemotherapy management, and post-transplant vigilance. However, they all share the feature of having a hospital for appropriate management of any emergency (Table 2).

Patients and donors

Patients who undergo outpatient HSCT are eligible regardless of diagnosis. Special consideration should be taken with a high disease risk index, that is, very small children, patients above 70 years, and

Table 1. Allogeneic hematopoietic stem-cell transplantation in an outpatient setting.

| Author, year | No. of transplants | Regimen | Type of transplant | Median Follow-up | OS | NRM | Completely outpatient (%) |
|--|--------------------|----------|--------------------------|-----------------------------|-----------------|-----------------|---------------------------|
| Gómez-Almaguer <i>et al.</i> , 2000 ¹ | 4 | NMA | Allo-HSCT | Not reported | Not reported | Not reported | 100% |
| Ruíz-Argüelles <i>et al.</i> , 2001 ⁴ | 26 | NMA | Allo-HSCT | Not reported | 42% (1 year) | Not reported | 81% |
| Svahn <i>et al.</i> , 2002 ⁵ | 36 | MAC | Allo-HSCT/ Haplo-HSCT | 15 months (1998–2000) | 70% (2 years) | 8% | Not reported |
| Svahn <i>et al.</i> , 2004 ³³ | 11 | MAC, NMA | Allo-HSCT | Not reported | Not reported | Not reported | 36.36% |
| Gutierrez-Aguirre <i>et al.</i> , 2014 ⁷ | 121 | RIC | Allo-HSCT | 54 months (2003–2009) | 59.1% (5 years) | Not reported | Not reported |
| Brammer <i>et al.</i> , 2015 ⁸ | 147 | NMA | Allo-HSCT | 3.2 years (2005–2011) | 60% (1 year) | 32% (2 years) | Not reported |
| Granot <i>et al.</i> 2019 ⁹ | 1,037 | NMA | Allo-HSCT | 12 months (1997–2017) | Not reported | 13% (5 years) | 47.15% |
| Guru Murthy <i>et al.</i> , 2019 ³ | 35 | RIC | Allo-HSCT | (2014–2017) | 82.8% | 10.8% (1 year) | 48.5% |
| Spinner <i>et al.</i> , 2019 ¹⁰ | 612 | NMA | Allo-HSCT | 6 years (2001–2016) | 42% (4 years) | 9% (1 year) | 57% |
| Gutiérrez-Aguirre <i>et al.</i> , 2020 ³⁴ | 111 | RIC | Allo-HSCT/ Haplo-HSCT | 6.6 months (2012–2017) | 46.7% | Not reported | 87% |
| Gutiérrez-García <i>et al.</i> , 2020 ³² | 41 | MAC, RIC | Allo-HSCT/ Haplo-HSCT | Not achieved (2015–2018) | 71% (1 year) | 23% at 1 year | 21.95% |
| Jaime-Perez <i>et al.</i> 2021 ³⁵ | 15 | RIC | Allo-HSCT/ Haplo-HSCT | 11 months (2006–2019) | 66.7% (1 year) | 29.6% at 1 year | 55.5% |
| Colunga-Pedraza <i>et al.</i> , 2021 ³⁶ | 60 | MAC | Haplo-HSCT | 12 months (2013–2019) | 38% (2 years) | 24.6% (1 year) | 21.6% |
| Murrieta-Álvarez and Ruiz-Argüelles 2021 ³⁷ | 20 | NMA | Haplo-HSCT | Not reported | 37.5% (2 years) | 35% | 55% |

Allo-HSCT, allogeneic hematopoietic stem-cell transplantation; Haplo-HSCT, haploidentical hematopoietic stem-cell transplantation; MAC, myeloablative conditioning; NMA, non-myeloablative; NRM, non-related mortality; OS, overall survival; RIC, reduced-intensity conditioning; TRM, treatment-related mortality.

patients with high blood component requirements, such as aplastic anemia. A specific chronological age limit should not be considered for transplantation, nor its outpatient conduct. Some centers consider patients over 65 years with an individualized geriatric evaluation.^{12,38} Good performance status is ideal (Karnofsky score $\geq 80\%$) with a preserved oral route, absence of serious comorbidities, and a hematopoietic cell transplantation-specific

comorbidity index (HCT-CI) of ≥ 3 as a relative contraindication for outpatient conduction. Furthermore, patients must temporarily reside close to the hospital, with guaranteed telephone access and the permanent presence of an educated caregiver throughout the process. After patient selection, related donors must be evaluated for harvest and remain at a residence near the hospital until a successful donation is achieved. In our

Table 2. Our centers' requirements for outpatient-based HSCT.

| |
|---|
| Patient |
| Age \leq 65 or individualized Karnofsky scale \geq 70 Preserved oral route Normal liver, cardiac, lung, and renal function Acceptance |
| Caregiver |
| Available 24 hours Appropriate educational level Phone access |
| Adequate patient's residence |
| Private room for the patient Near the hospital |
| Outpatient 7-day clinic |
| Chemotherapy and procedure rooms Hospital—day beds Laboratory reference Blood bank |
| Phone line available 24 hours/7 days Physician available 24 hours/7 days Hospitalization beds available 24 hours/7 days |
| HSCT, hematopoietic stem-cell transplantation. |

centers, both HLA-matched sibling donors (MSD) and haploidentical (haplo-HSCT) transplants are performed on an outpatient basis.^{12,37}

Caregivers and home

To successfully perform the procedure, the availability of at least a single educated and trained caregiver 24 hours a day is mandatory. Before the procedure, caregivers are taught to monitor signs and symptoms, assess patients' physical activity, nutrition, and sleep with their competence assessed through unstructured interviews.³⁹ They measure and report the patient's temperature at home if fever is suspected and document as well as communicate the incidence of other adverse effects at any hour of the day through a telephone emergency hotline connected directly to an HSCT professional. Caregivers are responsible for administering oral medications to the patient throughout the day, following defined nutrition requirements, arranging transportation, and maintaining continuous communication with the team.^{9,32}

We request that a bedroom and bathroom designated for the exclusive use of the patient with appropriate ventilation and illumination be available within the residence, that they avoid exposure to pets, indoor plants, and contact with other members of the residence, and try to do some exercise. Before the COVID19 pandemic, we recommended that both patient and caregiver refrain from going to public places and encouraged wearing surgical masks when leaving home to the outpatient center. After March 2020, we requested patients and caregivers isolate themselves 2 weeks before the procedure and encourage indoor masking within the residence if caregivers continued to have external contact with people other than the patient and the treatment center. When caregivers develop any symptoms suspicious of an upper respiratory infection, we ask that they leave the residence for appropriate testing and management;³⁶ meanwhile, another caregiver must be ready to help the patient.

Outpatient HSCT unit

Our outpatient facilities consist of a 7-day per week clinic with physician offices, chemotherapy infusion and procedure rooms, 'day-hospital' beds, and hematology reference laboratory, a cell processing facility, and a blood bank. The transplant team includes HSCT fellows, attending physicians, nurses, a nutritionist, a scheduler assistant, medical technicians, and a social worker. Notably, there are no advanced practice practitioners such as physician assistants or nurse practitioners in Mexico, and we have no pharmacists at our institution. The entire staff is involved in continuous medical education activities and training.^{9,12}

Patients come to the outpatient HSCT unit for evaluation, pre-transplant workup, and post-transplant follow-up and management. Single-patient examination rooms are a minimum requirement for the program's outpatient service. These rooms should be adequately equipped to allow clinical evaluation of patients. Infection control measures are necessary to minimize the risk of infection, including hand hygiene and the availability of an adequate room to isolate patients identified as a potential infectious risk to others. Ideally, a dedicated chemotherapy infusion area should be available, where patients can receive the conditioning regimen and cell infusion. A day hospital within the clinic is very useful. It can help

solve many common issues that arise during HSCT and avoid (or facilitate) hospitalization allowing that team to deliver IV fluids for dehydration, antiemetics, transfusions, and/or antibiotics while monitoring patients for several hours a day.⁴⁰ This day hospital can work 5–7 days a week in a standard or extended schedule according to different centers;^{41,42} however, the fundamental issue is the ability to provide emergency care either in the clinic itself or in the emergency room for care out of clinic hours to decide if the patient will be sent home with appropriate therapy or admitted to the inpatient unit. If an emergency department admission is needed, once the patient arrives is managed in an isolated room. In the case of stabilization, the patient is now admitted to the general ward and otherwise is transferred to the intensive care unit. The day hospital should have access to the inpatient HSCT unit. Alternatively, and perhaps ideally, an ‘away team’ can provide patient care physically at home, delivering supportive care without having to visit any center at all.

Some patients, especially those undergoing haplo-HSCT, will eventually require hospitalization, ranging from 52% to 88%.^{9,32} Most aspects of HSCT centers are well standardized by national guidelines such as FACT–JACIE. Hospital rooms could be, as in our center, standard, one-patient rooms not provided with high-efficiency particulate air (HEPA) filters, independent water filtration systems, nor positive pressure, but infection prevention measures must be very strict. Currently all patients and caregivers are SARS-CoV-2 tested before starting the transplant.

Conditioning and graft-versus-host disease prophylaxis

Conditioning regimens reported in completely outpatient HSCT include more frequently, non-myeloablative (NMA) or RIC regimens than myeloablative conditioning (MAC) due to their more favorable toxicity profile. We developed ‘the Mexican conditioning regimen,⁴³ which includes fludarabine (30 mg/m² for 3 days) and cyclophosphamide (Cy) (350 mg/m² for 3 days) plus either busulfan (4 mg/kg oral equivalent for 2–3 days) or melphalan (50–100 mg/m²/day for 2 days).¹² An alternative regimen reported in the outpatient setting is the use of NMA conditioning developed by Granot *et al.*,⁹ including fludarabine (30 mg/m²/day) from days –4 to –2 and 2–3 Gy

of TBI. Patients receive chemotherapy as outpatients and are discharged after the procedure. In the study by Svanh *et al.*, a MAC regimen consisted of Cy 60 mg/kg for 2 days, combined with 10 Gy of TBI; or fractionated TBI 3 Gy daily for 4 days. Another option was Bu (total dose 16 mg/kg) divided into four doses of 4 mg/kg per day combined with Cy 60 mg/kg for 2 days. In a few patients, RIC consisted of fludarabine 30 mg/m² per day for 6 days, combined with Bu 4 mg/kg per day for 2 days (total dose 8 mg/kg), combined with thymoglobulin 2 mg/kg per day for 4 days.⁵ Other centers use a model based on the ‘early discharge at-home regimen’. In this case, all patients receive conditioning and stem-cell infusion at the hospital and are discharged on day + 1 after cell infusion or the day after post-transplant cyclophosphamide (PT-Cy) (day + 5).³²

Graft-versus-host disease (GVHD) prophylaxis includes methotrexate (MTX) and calcineurin inhibitor for patients with MSD and patients with a haplo-HSCT donor, post-transplant Cy (50 mg/kg on days + 3 and +4), plus mycophenolic acid (2–3 g per day from +5 to +35) and a calcineurin inhibitor. Others use MTX on day + 1 at the hospital and then at home on days + 3, +6, and +11.³² Remarkably, there are no intravenous preparations of mycophenolic acid nor Cy or tacrolimus available in Mexico. For infection prophylaxis, oral levofloxacin (500 mg/day), acyclovir (400 mg/day), and itraconazole (100 mg/day) or voriconazole (200 mg PO BID) are administered to all patients from the onset of neutropenia until engraftment.¹¹ Cytomegalovirus (CMV) viral load is determined at day 14 and day 30 post-transplant and thereafter on a clinical basis according to each patient’s risk factors, including the development of GVHD, corticosteroid use, and prior reactivation, among others. No other viruses are monitored routinely. Red blood cell transfusions are given if patients present a Hb level below 7.0 g/dL or have significant symptoms and platelet apheresis with a platelet count threshold (Plt) < 20 × 10⁹/l or signs of bleeding.¹² Some centers administer RBC and platelets when counts are below 8.0 g/dL and 20 × 10⁹/L.³²

Hospital admission and follow-up

After cell infusion, patients are clinically evaluated daily, and laboratory exams are performed every 48 hours until engraftment. Caregivers and patients are instructed to contact the transplant

team if a temperature of 37.6°C or greater arises, as well as with the presentation of significant symptoms, such as vomiting, diarrhea, rash, neurologic alterations, or dyspnea, during chemotherapy administration or after transplantation. After neutrophil and platelet recovery, patients are evaluated weekly during the first 100 days, thereafter, according to physician judgment and the patient's condition.¹²

Hospitalization has been reported in 50%–80% of patients (Table 1), varying according to the patients' baseline characteristics, disease status, conditioning regimen intensity, and donor source. Patients are usually admitted due to neutropenic fever, infection, regimen-related toxicity such as mucositis, oral intolerance, diarrhea, and other complications. In the case of haploidentical grafts with PT-Cy, the occurrence of cytokine release syndrome (CRS), as defined by Lee *et al.*,⁴⁴ is a common indication, plus hemorrhagic cystitis; CMV viremia is more frequent in contrast to MSD with calcineurin inhibitor/methotrexate prophylaxis GVHD.¹¹

Haploidentical grafts: the next frontier

Haplo-HSCT has broken the HLA barrier and represents the only option for many people worldwide without access to a matched unrelated donor. The conduction of an outpatient haplo-HSCT is possible⁴¹ but definitively not easy nor exempt from risks. We recently described our experience in this regard. After analyzing our results, we found it feasible and safe; however, a more significant proportion of patients required short hospitalization with a median length of 8 days.¹² The presence of CRS represents the main limitation to full outpatient conduction; therefore, early recognition is crucial. In our study, most patients with non-relapse mortality (NRM) death had a high or very high Disease Risk Index, had active disease, or were beyond the second line of treatment. Therefore, this population should be extensively evaluated and maybe not considered a good candidate for outpatient care. Other potential complications to have in mind comprise a higher risk of graft failure compared to MSD HSCT, hemorrhagic cystitis, and cytomegalovirus reactivation.^{11,12}

Nevertheless, outpatient haplo-HSCT is feasible. At least partial outpatient care may be considered in most patients, including ambulatory conditioning with admission at day + 2 or + 3 when CRS

appears and an early discharge. Although minimal requirements to care haplo-HSCT do not differ from those described previously in MSD HSCT, a higher awareness of complications is needed.

Survival, outcomes, and morbidity

In recent years, some authors worldwide have reported the outcomes of allogeneic-HSCT on an outpatient basis with results comparable to those performed in-hospital (Table 1). The first publication regarding this kind of transplant appeared in 2000, where we reported the success of an NMA (non-myeloablative conditioning) regimen allo-HSCT in four patients allografted fully as outpatients.¹ Afterward, Ruiz-Arguelles *et al.* aimed to describe engraftment and graft failure in a cohort of 26 patients who underwent allo-HSCT with the NMA regimen. They found that three patients infused with $<5 \times 10^6/\text{kg}$ presented graft failure (11%).⁴⁵ In Sweden, Svahn *et al.*⁵ reported their experience when offering patients home care after conditioning, and interestingly 36/54 patients accepted the outpatient care. In this study, patients who were at home after transplant had lower transplantation related mortality rates (RR 0.22, $P=0.04$), and lower costs (RR 0.37, $P<0.05$) and in 2004 presented 11 MAC and NMA-transplanted patients of which 36.36% completed the procedure completely as outpatients.³³ In México, Gutierrez-Aguirre *et al.*⁷ reported a cohort of 121 patients who underwent RIC allo-HSCT in ABO-incompatible patients in the outpatient setting. Brammer *et al.*⁸ successfully administered an outpatient-based NMA conditioning regimen using Busulfan, Fludarabine, and Total Body Irradiation to 147 allo-HSCT in the elderly, finding suggesting this regimen as appropriate in patients age 65 and older or with an HCT-CI of 4 or greater. The largest study showing feasibility and safety was performed by Granot *et al.* from the Fred Hutchinson Cancer Research Center in 2019, reporting a cohort of 1,037 patients who underwent allo-HSCT with NMA conditioning using fludarabine and low-dose total-body radiation. Significant risk factors for hospitalization included unrelated transplants, 1 HLA antigen-mismatched transplant, and high HCT-CI scores. Significant risk factors for NRM were hospitalization, older age, unrelated transplants, and high HCT-CI scores. The main reasons for admission of this and other studies are presented in Table 3.⁹ In addition, Guru Murthy

Table 3. Causes of admission and non-relapse mortality in outpatient transplantation.

| Author, year | No. of transplants | Causes of admission | Non-Relapse Mortality causes |
|---|--------------------|---|---|
| Gómez-Almaguer <i>et al.</i> , 2000 ¹ | 4 | No admissions | No mortality |
| Ruiz-Argüelles <i>et al.</i> , 2001 ⁴ | 26 | aGVHD (n=1) | aGVHD (n=3) |
| Svahn <i>et al.</i> , 2002 ⁵ | 36 | Fever (n=24), no caregiver at home (n=2), diarrhea and/or fever and/or pain (n=3), pain (n=1), GVHD (n=1), nausea and vomiting (n=1), and mucositis (n=1) | aGVHD, and bacteremia |
| Svahn <i>et al.</i> , 2004 ³³ | 11 | Fever (n=7) No caregiver at home (n=1) | Acute haemorrhagic pancreatitis. |
| Gutierrez-Aguirre <i>et al.</i> , 2014 ⁷ | 121 | Not reported | Infection GVHD |
| Brammer <i>et al.</i> , 2015. ⁸ | 147 | Hepatic toxicity, veno-occlusive disease, cardiac failure, infections | infection/sepsis (n=17), aGVHD (n=8), cGVHD (n=10), cardiac failure (n=4), multisystem organ failure (n=2). |
| Granot <i>et al.</i> 2019. ⁹ | 1,037 | Infections, regimen-related toxicity, PBSC infusion, fever, GVHD, miscellaneous, cardiovascular, relapse/progression. | GVHD (n=116), adverse events related to treatment (n=40), age-related causes (n=33), infections (n=89), |
| Guru Murthy <i>et al.</i> , 2019. ³ | 35 | Fever (n=1), hypotension/acute kidney injury (n=1), seizure (n=1), tacrolimus toxicity (n=1), transaminitis (n=1), and mucositis (n=1) | Not reported |
| Spinner <i>et al.</i> , 2019. ¹⁰ | 612 | Infections (n=120), febrile neutropenia (n=94), aGVHD (n=16), Medication related (n=25), Neurologic complaint (n=23), Gastrointestinal complaint (n=21), Cardiac complaint (n=15), Electrolyte abnormality (n=7), Musculoskeletal (n=6), Pulmonary or endocrine complaint (n=9), other (n=15) | Not reported |
| Gutiérrez-Aguirre <i>et al.</i> , 2020. ³⁴ | 111 | Not reported | Sepsis (n=1), renal failure (n=1), infections, hemorrhagic cystitis (n=2), |
| Gutiérrez-García <i>et al.</i> , 2020.c | 41 | Mucositis (n=6), neutropenic fever (n=13), microbiological isolation (n=7), invasive <i>A. fumigatus</i> infection (n=1), CMV (n=22), acute renal failure (n=28) | GVHD (n=4), relapse (n=4), resistant CMV infection (n=1), relapse of previous melanoma (n=1), pulmonary embolism (n=1) |
| Jaime-Perez <i>et al.</i> 2021 ³⁵ | 15 | aGVHD (n=2), cGVHD (n=6), neutropenic fever (n=13), infection (n=13), positive CMV (n=5), mucositis (n=6), transfusion (n=14), relapse (n=4) | Infection (n=5), relapse/progression (n=2), bleeding (n=1), GVHD (n=2) |
| Colunga-Pedraza <i>et al.</i> , 2021. ³⁶ | 60 | CRS (n=32) Infection (n=11) Hemorrhagic cystitis (n=4), Mucositis (n=3) Gastrointestinal bleeding (n=1) | Sepsis (n=7) Hemorrhage (n=1) Cardiogenic shock (n=1) Pneumonia (n=2) Secondary graft failure (n=2) Hemorrhagic cystitis (n=2) |
| Murrieta-Álvarez and Ruiz-Argüelles 2021. ³⁷ | 20 | Febrile neutropenia (n=5) CRS (n=3) Intrabdominal abscess (n=1) | Sepsis (n=4) GVHD (n=2) Multisystem organ failure (n=1) |

aGVHD, acute graft *versus* host disease; CMV, Cytomegalovirus; CRS, Cytokine release syndrome; GVHD, graft *versus* host disease ; PBSC, Peripheral Blood Stem Cell.

*et al.*³ reported a retrospective study of patients who underwent RIC allo-HSCT, comparing the outcomes of 116 hospitalized patients and 35 patients. No differences in outcomes were observed between groups. Recently, Spinner *et al.* reported a cohort of 612 patients with different malignant hematologic diseases; 98% were transplanted as outpatients using non-myeloablative total lymphoid irradiation and antithymocyte globulin. This regimen was well tolerated with a low risk of GVHD and NRM. They observed durable remissions for hematologic malignancies, particularly for heavily pretreated lymphomas.¹⁰ In our center, we recently reported different outcomes of patients who underwent allo- and haplo-HSCT using MAC or RIC conditioning regimens on an outpatient basis achieving different outcomes of TRM, NRM, and hospitalization requirements^{11,12,35,37} (Table 1).

Is it possible to comply with regulatory standards in an outpatient setting?

The implementation of quality management systems in health services aims to guarantee the quality of the services provided, the safety of the people involved, and reduce costs. Hematopoietic cell transplantation is a process in which people from different areas participate (nursing, attending physicians, laboratory personnel, cell collection personnel, etc.), so it is very important to have written standard operating procedures that indicate ‘what’ and ‘how’ to avoid mistakes and ensure that all patients receive standardized treatment.

The Foundation for the Accreditation of Cellular Therapy (FACT) in America and the Joint Accreditation Committee ISCT-Europe & EBMT (JACIE) have established international standards for the provision of quality medical, nursing, and laboratory practice in the field of HSCT transplantation.⁴⁶ Information on the characteristics that the clinical unit should have is included in section B2 of the FACT standards manual in its seventh edition (March 2018). FACT considers that these characteristics may vary according to the number and type of transplant (autologous or allogeneic) performed, the cell source, epidemiological factors influencing the prevalence of opportunistic infections, and economic considerations.⁴⁷ For example, rooms with positive pressure filtration (HEPA) are

recommended for transplant patients; however, if not available, the unit must have infection control procedures, infection control audits and establish how single-patient rooms are assigned.

It is important to mention some of the characteristics of our transplant unit that help us comply with the FACT regulations (Table 2), including special tests like HLA typing, chimerism, among others. Currently, we perform most of our transplants on an outpatient basis, regardless of conditioning intensity and donor type. Very important in the development of the outpatient transplant unit are continuous training of the personnel and frequent results analysis. These requirements are fulfilled not only with attendance at courses and congresses but also with the scheduling of internal academic meetings where the members of the transplant unit can discuss clinical cases based on the medical literature (‘transplant board’). These meetings facilitate communication between members of the different areas. Concerning the analysis of results, all the members of the transplant unit must frequently meet to know the evolution of the patients (survival, incidence of GVHD, frequency of infections, adverse events, causes of death, causes of admission to the hospital) and evaluate the different stages of the transplant process to detect errors and areas of opportunity to develop an improvement plan. In addition, there must be a schedule of internal audits that evaluate the personnel’s adherence to the procedures of the transplant unit. Outpatient transplantation is not easy. It could be more complicated; therefore, quality standards must be fulfilled.

It is important to note that we built an outpatient HSCT unit with high-quality standards that allowed us to obtain the first FACT accreditation for this kind of outpatient-focused unit in Latin America in 2016, and we were re-accredited again in 2020, opening the door for this kind of outpatient HSCT units capable of fulfilling the FACT-JACIE quality standards.

Conclusions

International recommendations of HSCT in LMICs have been made, but with no comment regarding outpatient HSCT. To develop an HSCT program/unit, extensive financial, social, technical, and human resources are needed.

Moreover, physician, health authorities, politicians, nurses, and scientific society involvement is crucial for success.⁴¹ However, very few hospitals in LMIC are equipped with traditional HSCT units, and the existing units may not reach the required efficiency. In-hospital HSCT in many parts of the world is usually unaffordable and unrealistic option. Facing difficulties regarding institutions in Mexico and other LMICs, where developing a traditional HSCT unit is usually unrealistic and accompanied by economical, social and technical complications, outpatient HSCT emerges as an affordable, safe, and realistic option for patients dwelling in LMIC.^{40,42} The results of outpatient transplantation have never been directly compared with in-hospital procedures. However, reported experience has demonstrated feasibility. Infections could be less frequent and severe than in inpatient programs, and quality of life and food intake is improved when the patient stays home. However, there is room for improvement, and research areas of opportunity include home food and microbiota, caregiver training, patients' reported outcomes, quality of life issues, etc. In conclusion, building an outpatient HSCT unit with high-quality standards could be another way to improve the number of allo-HSCT procedures globally; therefore, we will witness the emergence of new therapeutic alternatives for patient management.

Author contributions

David Gómez-Almaguer: Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing.

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Conflict of interest statement

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