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ORIGINAL RESEARCH

Cost Assessment of Pediatric Haploidentical Hematopoietic Stem Cell Transplantation

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Purpose: Evaluate the costs related to the pediatric haplo-SCT and adult and pediatric geno-SCT at the CNGMO in order to establish a tailored reimbursement package by the Tunisian Health Insurance Fund.

Patients and Methods: This pharmaco-economic study compared the cost of pediatric haplo-SCT to adult and pediatric geno identical hematopoietic stem cell transplantation (geno-SCT) using the activity-based costing method. The cost assessment was conducted from the hospital's perspective and considered direct medical and non-medical costs.

Results: The cost assessment indicated that pediatric patients incurred higher expenses than adult patients. Furthermore, haplo-SCT was more expensive than geno-SCT for pediatric patients. The conditioning regimens used before haplo-SCT are more intensive than other preparative regimens and typically require longer inpatient therefore resulting in more costs. Complications, such as infections during the early phase of neutropenia and late-onset issues following hematopoietic stem cell transplantation (HSCT), particularly graft-versus-host disease (GVHD) and cytomegalovirus (CMV) reactivation, significantly contribute to increased procedural costs.

Conclusion: This study sets the standards for new specific packages for haplo-SCT and geno-SCT in pediatric patients.

Keywords: haploidentical, stem cell transplant, pediatric, cost

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) still remains a curative approach for patients with both malignant and non-malignant hematologic pathologies.[1]

However, access to allo-HSCT is often limited due to the timely availability of a suitable HLA-matched related donor or adequately HLA-matched unrelated donor, which requires a register search that results in a considerable delay from diagnosis to treatment. The use of haploidentical hematopoietic stem cell transplantation (Haplo-SCT) is on the rise and is becoming a standard treatment option for patients who lack a matched donor.[2]

However, this highly specialized medical procedure requires expensive medical resources.

In Tunisia, the National Bone Marrow Transplant Center [Centre National de Greffe de MoelleOsseuse (CNGMO)] has initiated haplo-SCT for pediatric patients in 2018. It should be noted that the CNGMO used to receive a reimbursement by the Tunisian Health Insurance Fund [Caisse Nationale d'Assurance Maladie (CNAM)] for each HSCT, within a fixed global package amounting to $27,347 (2019 US Dollars) for geno identical hematopoietic stem cell transplantation (geno-SCT) and haplo-SCT for both adult and pediatric patients. The package covers all the necessary medical resources within the first year following the transplantation, including managing the complications.

Several studies have examined the financial impact of geno- and haplo SCT in adult patients. However, to our knowledge, no studies have been conducted on the pediatric population, either in Tunisia or elsewhere. The present study aims to evaluate the costs related to the pediatric haplo-SCT and pediatric and adult geno-SCT at the CNGMO in order to establish a tailored reimbursement package by the CNAM.

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Materials and Methods

This is a descriptive pharmacoeconomic study carried out using the activity-based costing method. The cost assessment was conducted from the hospital's (CNGMO) perspective included direct medical and non-medical costs from transplant up to 1 year. The monetary valuation was based on 2019 US Dollars.

First the process of HCT has been broken down into a sequence of activities that take part throughout the first year of this procedure. Thus, costs were divided into three phases: pre-transplantation, initial hospitalization, and follow-up:

The pre-transplantation phase included donor and recipient laboratory testing, graft harvesting and treatment.

The initial hospitalization phase included the full hospitalization in the transplant unit, conditioning protocols (Table 1), parenteral nutrition and hydration products, medical devices, investigations and biological tests and blood products (BPs) administration.

Table 1 Frequencies of the Conditioning Regimens

Protocols	Protocol Cost (US$)	Frequency per Year	Average Cost According to Frequency (US$)
Pediatric Haplo-SCT			
Protocol 1: Thiotepa, Busulfan, Fludarabine, Cyclophosphamide	21,489	24%	5157
Protocol 2: Thiotepa, Fludarabine, Busulfan, Anti thymocyte globulin	30,487	8%	2439
Protocol 3: Busulfan, Fludarabin, Cyclophosphamide	20,736	32%	6636
Protocol 4: Rituximab, Fludarabine, Busulfan, Antithymocyte Globulin (Rituximab in pre-treatment)	26,868	20%	5374
Protocol 5: Aplastic anemia – Antithymocyte Globulin	25,000	16%	4000
Total Average	24,916	100%	23,606
Pediatric Geno-SCT			
Protocol 1: Thiotepa, Busulfan, Fludarabine	16,331	31%	5063
Protocol 2: Antithymocyte Globulin, Fludarabine, Busulfan	19,686	8%	1575
Protocol 3: Busulfan, Fludarabine	10,543	26%	2741
Protocol 4: Fludarabine, Cyclophosphamide	4951	9%	446
Protocol 5: Antithymocyte Globulin, Fludarabine, Cyclophosphamide	10,469	3%	314
Protocol 6: Aplastic anemia – Antithymocyte Globulin	13,464	6%	808
Protocol 7: Thiotepa, Antithymocyte Globulin, Fludarabine, Busulfan	18,935	17%	3219
Total Average	13,483	100%	14,165
Adult Geno-SCT			
Protocol 1 ALL Etoposid + Total Body Irradiation	2677	14%	375
Protocol 2 AML Cyclophosphamid Total Body Irradiation	2730	17%	464
Protocol 3 ALL Thiotepa Busulfan Fludarabine	19,276	17%	3277
Protocol 4 AML Fludarabine Busulfan Antithymocyte globulin (rabbit)	15,144	4%	606
Protocol 5 AML Busulfan Cyclophosphamid	8797	21%	1847
Protocol 6 Anemia of Fanconi Fludarabine	9112	2%	182

(*Continued*)

Table 1 (Continued).

Protocols	Protocol Cost (US$)	Frequency per Year	Average Cost According to Frequency (US$)
Protocol 7 Aplastic Anemia Antithymocyte globulin (equine)	9095	13%	1182
Protocol 8 Aplastic Anemia Antithymocyte globulin	9689	4%	388
Protocol 9 Antithymocyte globulin (rabbit) Melphalan	16,024	8%	1282
Total Average	10,283	100%	9603

Abbreviations: ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; Geno-SCT, Geno identical hematopoietic stem cell transplantation; Haplo-SCT, Haplo identical hematopoietic stem cell transplantation.

The follow-up phase included outpatient consultations, imaging, laboratory test, the full hospitalization, medication and blood products administration. It also included complication treatment for Graft Versus Host Disease (GVHD) and cytomegalovirus reactivation (CMV) as well as post-acute care.

The cost evaluation excluded the costs of relapse.

The cost of biological analysis (virology, bacteriology, hematology, and biochemistry) was obtained through the national codification system for public structures, where each test code is assigned a specific price. The prices of medicines were collected from supplier invoices. In order to calculate the recommended drug dosages, a weight of 40 kilograms and a body surface of 1.28 m2 were assumed as mean parameters. The cost of conditioning protocols was calculated for each type implemented by adult and pediatric units. A Frequency-weighted average protocol cost was considered according to the frequencies of protocols used in 2019. The cost of medical devices was determined using the prices negotiated through the tender conducted by the CNGMO. A mean hospital length of stay is 45 days for adult allo-HSCT, 60 days for pediatric allo-HSCT and 90 days for Haplo-SCT according to previous studies made in the center.[3] The cost per hospitalization day was assessed by considering the average salaries of medical and paramedical staff, the estimated time each category of staff spends with the patient, catering and patient meals, and general expenses including gas, electricity, sterilization, hygiene materials and maintenance (the annual maintenance expenses were divided by the number of hospitalization days in the adult or pediatric unit). In the follow-up phase, costs were estimated for patients without complications as well as for those with complications related to GVHD and CMV reactivation occurring separately or together. The total follow-up cost was estimated considering the frequency of each complication.

Results

The cost assessment showed that Pediatric geno-SCT is more expensive than the adult and that pediatric haplo-SCT cost is significantly higher. Indeed, the total estimated costs were $58,440 for adult geno-SCT, $86,446 for pediatric geno-SCT and $111,303 for pediatric haplo-SCT. Table 2 shows the costs included in the different phases of the procedure for the adult and pediatric geno-SCT and haplo-SCT.

Table 2 Adult and Pediatric Geno-SCT and Haplo-SCT Discounted Costs from Transplant up to 1 year in US Dollars

	Adult Geno-SCT	Pediatric Geno-SCT	Pediatric Haplo-SCT
General Assumptions			
Mean Weight (Kg)	70	40	40
Body surface (m2)	1.8	1.28	1.28
Mean hospital length stay (days)	45	60	90

(*Continued*)

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Table 2 (Continued).

	Adult Geno-SCT	Pediatric Geno-SCT	Pediatric Haplo-SCT
Activities			
Pre-transplantation			
Donor and recipient testing	874	961	966
Grafts procurement	1814	518	518
Graft treatment	673	–	–
Pre-transplantation total	3361	1479	1484
Initial hospitalization			
Medical devices	337	529	653
Conditioning regimen (Frequency-weighted average protocol cost)	9603	14,165	23,606
Hydration products	539	511	663
Laboratory testing, exploration and transfusion	6092	6864	9186
Febrile neutropenia treatment	8584	16,841	17,286
Hospitalization costs	11,261	15,017	22,525
Initial hospitalization total	36,415	53,927	73,919
Follow up			
Without Complication	10%	10%	10%
Consultations	263	239	215
Laboratory tests	2091	3456	3257
Medicines	1593	10,770	10,188
Follow-up without complications total	3946	14,466	13,660
GVHD positive	25%	25%	25%
Consultations	263	239	215
Laboratory tests	2091	3456	3257
Medicines	7625	12,364	16,862
Follow up with complication (GVHD) total	9978	16,059	20,334
CMV positive	20%	20%	20%
Consultations	263	239	215
Laboratory tests	2091	3456	3257
Medicines	12,918	27,047	29,187
Hospitalization costs	4418	5941	5941
Follow up with complication (CMV) total	19,689	36,684	38,600
GVHD positive and CMV positive	45%	45%	45%
Consultations	263	239	215

(*Continued*)

Table 2 (Continued).

	Adult Geno-SCT	Pediatric Geno-SCT	Pediatric Haplo-SCT
Laboratory tests	2091	3456	3257
Medicines	19,532	30,901	38,878
Hospitalization costs	4418	5941	5941
Follow up with complication (GVHD& CMV) total	26,303	40,538	48,291
Follow up cost total	18,663	31,040	35,901
Total estimated Cost	58,440	86,446	111,303

Abbreviations: GVHD, Graft-versus-host disease; CMV, Cytomegalovirus; Geno-SCT, Geno identical hematopoietic stem cell transplantation; Haplo-SCT, Haplo identical hematopoietic stem cell transplantation.

Pre-transplantation costs accounted for 6%, 2% and 1% for adult geno-SCT, pediatric geno-SCT and Pediatric haplo-SCT, respectively. Initial hospitalization phase was the costliest one and represented 62%, 62% and 66% of the total estimated cost for adult geno-SCT, pediatric geno-SCT and Pediatric haplo-SCT, respectively.

The costs of the follow-up phase exhibit significant variability depending on the occurrence of GVHD or CMV complications. As shown in Table 2, these costs can range from $13,660 without complications to $48,891 for patients with both GVHD and CMV.

Discussion

Haplo-SCT has become a significant treatment option for patients lacking a fully matched donor. This evaluation aim to assess the costs related to the pediatric haplo-SCT and pediatric and adult geno-SCT at the CNGMO in order to establish a tailored reimbursement package by the CNAM. In this study, we employed an activity-based costing method, which is considered the most common analytical approach in costing methodologies in health care because it provides a more detailed and accurate view of costs and therefore a better decision-making.[4]

Our cost assessment revealed that pediatric geno-SCT is more expensive than adult geno-SCT, and that the cost of pediatric haploidentical SCT (haplo-SCT) is significantly higher than both. Specifically, the total estimated costs were $58,440 for adult geno-SCT, $86,446 for pediatric geno-SCT, and $111,303 for pediatric haplo-SCT. The higher cost of pediatric haplo-SCT can be largely attributed to two main factors: the use of more expensive syrup formulations, which are necessary for young patients unable to take standard tablets, and a longer duration of hospitalization required for haploidentical procedures.

Several studies were conducted in the adult population, notably the one carried out in 2013, which estimated the direct costs of allograft during the first-year post-transplant.[5] Another study conducted at the same center estimated the direct costs during the second year post-allograft.[5] A retrospective analysis conducted in Marseille assessed the cost-effectiveness of haplo-SCT compared to matched unrelated donor transplantation in patients over 55 years old with hematological malignancies. The study found that haplo-SCT was more cost-effective, with a mean overall survival of 19.4 months and a mean cost of $108,134 compared to 15.1 months and $166,510 for matched unrelated donor transplantation. The incremental cost-effectiveness ratio was $163 per life year gained. In another study, researchers analyzed the costs of haplo-SCT, matched related donor (MRD), and matched unrelated donor (MUD) transplants. They found that the pre-transplant costs for MUD were significantly higher ($38) compared to MRD ($16) and haplo-SCT ($18). During the transplant phase, haplo-SCT incurred higher costs due to longer hospital stays and increased medication use. Overall, the total costs for haplo-SCT ($124) were similar to those for MUD ($127).[6]

These studies indicate that while haplo-SCT may have higher upfront costs, particularly during the transplant phase, it can be a cost-effective option, especially when considering the availability of donors and the potential for improved survival outcomes.

Table 3 Coverage Packages Agreed Upon Between the CNGMO and the National Health Insurance (CNAM) in 2020

Coverage Packages Reviewed by the CNAM (US$)	Adult Geno-SCT	Pediatric Geno-SCT	Pediatric Haplo-SCT
Transplantation (up to 3 months)	4091	27,957	39,549
Follow-up period (1 year following discharge post-transplant)	24,547	11,592	13,637
Total coverage package excluding complications medicines	28,639	39,549	53,186

Abbreviations: Geno-SCT, Geno identical hematopoietic stem cell transplantation; Haplo-SCT, Haplo identical hematopoietic stem cell transplantation.

Furthermore, several studies have evaluated the efficacy and safety of haploSCT in pediatric patients. In 2021 study in Frontiers in Pediatrics compared haplo-SCT with geno-SCT in children with acute leukemia. The retrospective analysis found no significant differences in treatment outcomes, suggesting that haplo-SCT is a viable alternative to matched donor transplants.[7] Another study, published in Bone Marrow Transplantation journal, evaluated the feasibility of haplo-SCT with post-transplantation cyclophosphamide (PTCy) in children with advanced pediatric malignancies. The research indicated that this approach is well-tolerated and can be performed universally, offering a promising treatment option for this patient group.[8]

However, most studies focus on the clinical outcomes, survival rates, and complications associated with children haplo-SCT, and no cost estimation study has been conducted worldwide. This makes our study unique and crucial, as it not only addresses an important gap in the literature but also provides valuable data to evaluate the cost-effectiveness and economic sustainability of haplo-SCT.

This cost assessment contributed to an update in the reimbursement policy by the CNAM, leading to individualized reimbursement amounts for each type of transplantation (see Table 3). The newly defined coverage system includes two main components:

A basic reimbursement package, which comprises two phases:

- The transplantation phase, covering the pre-transplant period and the initial hospitalization, lasting up to three months.
- The follow-up phase, which extends up to one year following the end of the initial hospitalization. This phase includes the core post-transplant treatments such as immunosuppressive therapy, antimicrobial prophylaxis, growth factors, and other necessary supportive care but no complications (CMV, GVH, Neutropenia, …)

A complications reimbursement package, designed to cover the costs associated with the management of post-transplant complications up to one year post transplantation. This is handled through a separate billing mechanism between the transplant center and the CNAM, allowing for additional invoices—particularly for medications used in treating complications not covered by the basic package.

This distinction was necessary due to the high frequency and varying likelihood of post-transplant complications (such as CMV positive GVHD positive, CMV positive, GVHD positive, or cases without complications).

Nevertheless, this study presented some limitations. It was conducted shortly after the implementation of haploidentical transplantation in our center. As a result, the study was performed using the ABC method with an insufficient follow-up of real-world data. Further studies can be conducted with a larger number of patients and by including other perspectives (societal, etc).

Conclusion

The cost assessment showed that pediatric patients had higher costs than adult patients and that haplo-SCT is more expensive than geno-SCT for pediatric patients. This can be partly attributed to the longer average length of initial hospitalization for pediatric haplo-SCT compared to both pediatric and adult geno-SCT. Conditioning regimens for

haplo-SCT are more intensive than other preparative regimens and generally require longer inpatient stays and thus increasing costs. Complications, such as infections during the early phase of neutropenia and late-onset complications following hematopoietic SCT, particularly GVHD and CMV reactivation, contribute to increased procedural costs.

By quantifying the costs involved, our study will help in comparing haplo-SCT with other forms of transplantation, especially in low-resource settings where financial considerations are particularly important.

This study facilitated the establishment of new specific packages for geno-identical and haplo-identical hematopoietic stem cell transplantation in pediatric patients. Furthermore, the package for pediatric haplo-SCT has nearly doubled from the initially applied $27,347. Additionally, medications for complications can be invoiced separately from the packages based on actual usage for each patient. Future research should compare the estimated costs using activity-based costing with real-world costs.

Abbreviations

CNGMO, National Bone Marrow Transplant Center; CNAM, the Tunisian Health Insurance Fund; allo-HSCT, Allogeneic hematopoietic stem cell transplantation; Haplo-SCT, Haploidentical hematopoietic stem cell transplantation; Geno-SCT, Genoidentical hematopoietic stem cell transplantation.

Ethical

No ethical approval or review by an institutional review board (IRB) or ethics committee was required for this research.

Disclosure

The authors report no conflicts of interest in this work.

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