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Impact of the Mexican universal healthcare *Seguro Popular* on hematopoietic stem cell transplantation: Experience of a national health institute.

Efecto del Seguro Popular en el trasplante de células progenitoras hematopoyéticas: experiencia de un instituto nacional de salud

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Abstract

BACKGROUND: In 2004, a Universal Healthcare System was established in Mexico in order to protect most patients from catastrophic expenditures. Hematopoietic stem cell transplantation (HSCT) has been covered since 2015 at our center, a national health institute.

OBJECTIVE: To analyze the impact of the *Seguro Popular* in HSCT in adults at one of the referral centers of this system.

PATIENTS AND METHOD: A retrospective analysis of patients undergoing HSCT with and without financing by the *Seguro Popular* at a national institute of health in Mexico City performed from January 2011 to December 2018.

RESULTS: There were included 194 patients. The mean number of HSCT performed annually before and after *Seguro Popular* was similar. No differences were observed in non-relapse mortality. The 2-year disease-free survival and overall survival were similar before and after *Seguro Popular* for both, autologous and allogeneic/haploidentical HSCT.

CONCLUSIONS: Although *Seguro Popular* has eliminated some important expenses generated mainly by the in-patient procedure, it still has deficiencies that should be solved in order to achieve an optimal universal healthcare coverage in Mexico. Further studies should be performed focusing on other expenses and more importantly, the other two affiliated centers to the *Seguro Popular* should publish their results for further comparisons.

KEYWORDS: Hematopoietic stem cell transplantation; Mexico; Universal healthcare.

Resumen

ANTECEDENTES: El 50% de los mexicanos vive en pobreza, por lo que la seguridad social es limitada. Sin embargo, a partir de 2004 se estableció un sistema universal de salud para proteger a los pacientes de gastos catastróficos. El trasplante de células progenitoras hematopoyéticas comenzó a ser subsidiado 11 años después en nuestro centro.

OBJETIVO: Analizar el efecto del Seguro Popular en pacientes adultos a quienes se les efectuó trasplante de células progenitoras hematopoyéticas en uno de los tres centros de referencia de este programa.

PACIENTES Y MÉTODO: Análisis retrospectivo de pacientes a los que se les hizo trasplante de células progenitoras hematopoyéticas con y sin el Seguro Popular en el Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, efectuado de enero de 2011 a diciembre de 2018.

RESULTADOS: Se incluyeron 194 pacientes. El promedio de trasplantes de células progenitoras hematopoyéticas realizados por año antes y después del Seguro Popular fue similar. No se encontraron diferencias en mortalidad asociada con el trasplante. Asimismo, la supervivencia libre de enfermedad y la supervivencia global a dos años

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fueron similares entre ambos grupos, tanto en TCPH autólogos como alogénicos/haploidénticos.

CONCLUSIONES: Aunque el Seguro Popular ha eliminado gastos importantes para los pacientes, sobre todo durante la hospitalización, aun tiene deficiencias que deben ser resueltas para alcanzar una cobertura óptima y se requieren más estudios para hacer comparaciones.

PALABRAS CLAVE: Trasplante de células progenitoras hematopoyéticas; México; Cobertura universal.

INTRODUCTION

In Mexico, 55.6 million people, accounting approximately 44% of the total population lives in poverty;[1] therefore, as a consequence, health care coverage is scarce. In 2004, the Social Protection System in Health Project, which started as a reform to the General Health Law in 2003, lead to the creation of the Social Protection in Health System, making universal health coverage mandatory in Mexico, aiming to promote a reduction in the catastrophic health spending of patients and families and to create an equitable and accessible medical healthcare.[2,3] This Universal Healthcare Program supported the expansion of the Catastrophic Expenses Protection Fund (FPGC, by its acronym in Spanish) as part of the *Seguro Popular* (SP). At the beginning, acute lymphoblastic leukemia in children and breast and cervical cancers in adults were exclusively included as part of the oncological specialized diseases within the FPGC. Two years later (2006), all childhood malignancies were covered, along with hematopoietic stem cell transplantation (HSCT) in this age group; however, it was not until 2011, when HSCT in adults was included. In this setting, prior 2011, nationwide, undergoing a HSCT was more complicated for Mexican adult patients due to paucity of coverage as social security systems are usually limited to a proportion of the retired population and Mexicans with formal employment or private insurances.[4,5] Nonetheless, as previously published by our group,[6] HSCT is a relatively inexpensive procedure in Mexico compared to other developing countries, and therefore, it might seem to be potentially attainable for most Mexican adult patients, as expenses to bear the cost of hospitalization (20% to 60% of the total HSCT cost),[6] including some medications and in-patient studies (laboratory, imaging), or supportive therapy such as transfusions, rarely remained a barrier at our center. Accordingly, prior the approval of the financial subsidy from the SP for HSCT (affiliation in 2011 for breast cancer) at our center in Mexico City, a National Institute of the Mexican Ministry of Health, HSCT were performed as a result of the partial institutional subsidy and the establishment of a non-governmental organization (NGO) in 2002.[7] The institutional subsidy for in-patient hospitalization and some associated expenses as well as further outpatient consultations was categorized by an assigned socioeconomic classification after an interview with the Department of Social Work, making these services low or competitive according to patients' incomes; and the NGO *Unidos, Asociación Pro Trasplante de Médula*

Ósea Francisco Casares Cortina, A.C., subsidized chemotherapy, immunosuppression, and other medications required for the procedure.[7]

However, currently, with the affiliation to the *Seguro Popular*, the cost of HSCT including the in-patient procedure, along with the required services and medications, does not represent an expense for the patient. More importantly, to date, there is scarcity of statistics reporting the outcomes of HSCT after the establishment of the *Seguro Popular*, thus, the objective of this study was to analyze the impact of the Mexican Universal Healthcare *Seguro Popular* (SP) in hematopoietic stem cell transplantation (HSCT) in adult patients at one of the referral centers.

PATIENTS AND METHOD

Patients

A retrospective analysis of adult patients undergoing HSCT four years before (January 2011-December 2014) the affiliation to the SP and after this affiliation (January 2015-December 2018) at a national institute of health in Mexico City. All institutional patients without any health care coverage were candidates to affiliate to the SP. Patients undergoing HSCT without subsidy from the SP after the affiliation in 2015, were excluded from the analysis (n = 17). The data for this study derived from patients' information collected prospectively in the database of the HSCT Program, the Institutional electronic records, and the Institutional database of the SP.

HSCT procedure

For autologous HSCT, hematopoietic stem cells (HSCs) were collected by peripheral blood apheresis and for most allogeneic (allo) transplantations by multiple aspirations of the iliac crests (bone marrow). All patients were admitted in rooms with high-efficiency particulate air (HEPA) filters 1 day prior the beginning of the conditioning regimen. According to the underlying disease, most autologous HSCT patients were conditioned with BEAM (carmustine 300 mg/m^2, IV, etoposide 800 mg/m^2, IV, cytarabine 1000 mg/m^2, IV, melphalan 140 mg/m^2, IV), standard BUCY2 (busulfan 16 mg/kg, oral and cyclophosphamide 120 mg/kg, IV), MEL-200 (melphalan 200 mg/m^2, IV), or etoposide and carboplatin (1200 mg/m^2, IV and 1500 mg/m^2, IV). Most patients undergoing allogeneic HSCT received reduced BUCY2 (busulfan 12 mg/kg, oral and cyclophosphamide 80 mg/kg, IV), followed by standard BUCY2, and reduced intensity regimens (RIC) (fludarabine 120-180 mg/m^2, IV and busulfan 16 mg/kg, oral). The conditioning regimen for aplastic anemia included cyclophosphamide (200 mg/kg, IV) with or without antithymocyte globulin (ATG) (60 mg/kg, IV). Graft-*versus*-host disease (GVHD) prophylaxis, antimicrobial therapy (prophylactic and empiric), nutritional support, and transfusions were provided according to institutional and international guidelines.

Outpatient follow-up

When platelet and neutrophil engraftment was observed and in the absence of infections or complications, patients were discharged. For allogeneic HSCT follow-up, patients underwent weekly outpatient consultations during four months. Labs taken during every visit included: complete blood count (CBC), CMV antigenemia, cyclosporine levels, comprehensive metabolic panel (CMP), and magnesium. Chimerism was performed once monthly for 6 months. Medications included trimethoprim-sulfamethoxazole, acyclovir, cyclosporine A, omeprazole, and magnesium. For autologous outpatient follow-up, visits took place twice a month during the first four months. Requested labs included CBC and liver panel; no medications were prescribed for these patients.

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Definitions and endpoints

Non-relapse mortality (NRM) was defined as death related to the conditioning regimen, infections during aplasia or under immunosuppressive treatment, or associated with the development of GVHD, without relapse or progression and excluding causes due to underlying disease. Disease-free survival (DFS) was established as the length of time from transplantation until relapse or progression of the underlying disease. Overall survival (OS) was defined as time from transplantation until death from any cause.

Statistical analysis

Categorical variables were described by frequencies and percentiles. Continuous variables were described by the median and interquartile range using the frequency analysis. Patients were dichotomized before and after the affiliation to the SP and number of HSCT, GVHD, NRM, DFS, and OS were compared between the two groups. The DFS and OS were calculated using the Kaplan Meier estimator. Cumulative incidence estimates were calculated for other endpoints (NRM, relapse, GVHD) to account for competing risks. SPSS v.21 (IBM, Chicago, IL) was used.

RESULTS

HSCT before SP (2011-2014)

Ninety-seven HSCT were performed from January 2011 to December 2014, with a mean of 24 HSCT annually. Most were autologous (n = 55, 57%) and the remaining 42 were allogeneic (45%). Most patients were males (n = 53, 55%). The median age was 36 years (range, 18-62) for the entire group. The most frequent underlying diseases were lymphomas (n = 26, 47%) and acute leukemias (n = 14, 33%) for autologous and allogeneic HSCT, respectively. Overall characteristics are described in **Table 1.**

HSCT after SP (2015-2018)

The number of HSCT performed from January 2015 to December 2018 were 97, and consequently a mean of 24 HSCT per year. Sixty-two percent (n = 60) were autologous, 23% (n = 22) were allogeneic, and 15% (n = 15) were haploidentical. Male was the most frequent gender in all the group (n = 51, 53%). The median age for all the group was 35 years (range, 19-64). For autologous and allogeneic/haploidentical HSCT the most frequent underlying diseases were multiple myeloma (n = 22, 37%) and acute leukemias (n = 26, 70%), respectively. Overall characteristics are described in **Table 1**.

Outcomes before and after SP

Table 2 shows the overall results before and after SP by type of HSCT. The mean number of HSCT performed annually before and after SP was similar: 14 and 15 autologous HSCT and 10 and 9 allogeneic HSCT, respectively. Accounting allogeneic and haploidentical HSCT, acute and chronic GVHD were higher in patients undergoing the procedure before SP; however, no statistically significant differences were observed, 45% *vs* 23% (p = 0.06) and 50% *vs* 38% (p = 0.5), respectively. No differences were observed in non-relapse mortality. The 30-days, 100-days, and 1-year NRM in autologous HSCT was 0% *vs* 2% (p = 0.5), before and after SP, respectively. Thirty-day, 100-day, and 1-year NRM in allogeneic/haploidentical HSCT was slightly higher after SP compared to before SP; however, no statistically significant differences were observed: 3% *vs* 0% (p = 0.4), 15% *vs* 6% (p = 0.3), and 21% *vs* 19% (p = 0.3), respectively. The 2-year DFS was similar before and after SP for both, autologous and allogeneic/haploidentical HSCT, 50% *vs* 56% (p = 0.2) and 66% *vs* 48% (p = 0.9), respectively. The 2-year OS in autologous HSCT before and after SP was 79% *vs* 91% (p = 0.02), respectively, and it was 55%

Table 1. Patient demographics and clinical characteristics

Type of HSCT	Autologous		Allogeneic/haploidentical	
	Before SP n (%)	After SP n (%)	Before SP n (%)	After SP n (%)
Total HSCT	55	60	42	37
Gender				
Male	34 (62)	35 (58)	17 (40)	18 (49)
Female	21 (38)	25 (42)	25 (60)	19 (51)
Median age (range)	36 (16-64)	39 (20-64)	36 (18-63)	28 (19-57)
Underlying disease				
Aplastic anemia	-	-	3 (7)	7 (19)
Acute lymphoblastic leukemia	1 (1)	1 (2)	8 (19)	20 (54)
Acute myeloid leukemia	2 (4)	6 (10)	6 (14)	6 (16)
Lymphomas	26 (47)	20 (33)	4 (10)	1 (3)
Myelodysplastic syndrome	-	-	7 (17)	-
Multiple myeloma	13 (24)	22 (37)	-	-
Others	13 (24)	11 (18)	14 (33)	3 (8)
HSC source				
Bone marrow	1 (2)	-	22 (52)	31 (84)
Peripheral blood stem cells	54 (98)	60 (100)	20 (48)	6 (16)
Conditioning regimen				
Myeloablative	55 (100)	48 (80)	7 (17)	-
Reduced intensity	-	-	35 (83)	29 (78)
Non-myeloablative	-	12 (20)	-	8 (22)

SP: *Seguro Popular*.

vs 58% (p = 0.8) in allogeneic/haploidentical HSCT, respectively.

DISCUSSION

The key financing elements within the establishment of the *Seguro Popular* were access to publicly-funded health insurance for all Mexican families and to provide a package of personal health services based on cost-effectiveness and burden of diseases. In this context, the federal and state governments finance the SP, however, some patients and their families also contribute with a small annual co-payment according to their financial status assigned during the affiliation process[8] and families classified in the first two income deciles are exempted from co-payments.[9]

To determine how the SP has affected the health of the registered population, the program carried out an in-depth evaluation collaborating with researchers from national and international universities.[10-14] These reports highlighted that registration to the SP increased the probability of Mexican families to visit a primary care center with an increase of up to 30% in the number of medical appointments. Further, the University of Chicago[15] carried out two analyses to estimate the effect of the SP on catastrophic out-of-pocket

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Table 2. Outcomes before and after *Seguro Popular*

	Autologous			Allogeneic/haploidentical		
Outcomes	**Before SP**	**After SP**	**p**	**Before SP**	**After SP**	**p**
Mean number of HSCT (annually)	14	15	0.5	10	9	0.5
GVHD						
Acute	N/A	N/A	-	45%	23%	0.06
Chronic				50%	38%	0.5
NRM						
30 days	0%	2%	0.5	0%	3%	0.4
100 days	0%	2%	0.5	6%	15%	0.3
1 year	0%	2%	0.5	19%	21%	0.3
Survival						
2-year DFS	50%	56	0.2	66%	48%	0.9
2-year OS	79%	91%	0.02	58%	55%	0.8

DFS: disease-free survival; GVHD: graft-*versus*-host disease; HSCT: hematopoietic stem cell transplantation; N/A: not applicable; NRM: non-relapse mortality; OS: overall survival; SP: *Seguro Popular*.

health expenditures for rural and urban areas. The authors concluded that this program had reduced expenses in both, urban and rural areas, the latter depending on access to healthcare facilities. However, those were general estimations of the SP and to date, no evaluations have been performed to determine the impact in HSCT. Thus, this is the first study reporting the experience of a center performing this procedure in Mexico with funding from the SP. The first HSCT financed by the SP at our institution was performed in February 2015. Moreover, although there are approximately twelve public, well-established referral centers performing HSCT in adults in Mexico, half belonging to the Ministry of Health and therefore affiliated to the SP, currently, three centers including our institution (the National Cancer Institute in Mexico City and the University Hospital in Monterrey), have been actively performing HSCT in adults for at least 4 years.

Our results showed that the mean number of HSCT performed annually before and after SP were similar. More importantly, the 30-day, 100-day, and 1-year NRM was similar in autologous HCST before and after SP. Despite a slightly higher NRM observed in allogeneic/haploidentical HSCT before SP, no statistically significant differences were observed. Accounting allogeneic and haploidentical HSCT, both, acute and chronic GVHD were similar before and after SP. Moreover, the 2-year DFS was similar and no statistically significant before and after SP in both autologous and allogeneic/haploidentical HSCT. The 2-year OS was similar in allogeneic/haploidentical HSCT, and although the 2-year OS was higher and statistically significant in autologous HSCT, this should be considered discretely as diagnoses differed, for instance the number of patients with multiple myeloma was higher after SP compared to before SP (22 vs 13, respectively). Overall, despite including a small number of patients in the preliminary analysis of our Institutional affiliation to the SP, practices have not changed since the restructuration of our HSCT Program in 1998, hence, results throughout the years have been similar. Moreover, we have previously published the experience of our HSCT Program,[16] indicating that

the outstanding outcomes we have obtained thus far were mostly a consequence of the availability of medications due to the creation of the NGO Unidos, which differs from the comparisons made in other malignancies, specifically breast cancer,[17] as SP has helped to establish efficient standardized mechanisms to treat those patients and has included monoclonal antibodies within its coverage.

Also, according to our previously published HSCT costs:[6] 12,155 USD and 18,260 USD, for autologous and allogeneic HSCT, respectively, although the SP has benefited Mexican patients undergoing this procedure by reducing these costs to basically zero, it still presents limitations that are important in developing countries. One of the main disadvantages is the restraint within the financial support within the patients' follow-up. As it is widely known, patients undergoing HSCT, especially allogeneic transplantation, require indefinite, frequent consultations in the outpatient setting after the procedure and immunosuppressive therapy; the SP has not included these expenses within the budget (three stages of healthcare: in-patient procedure, GVHD, hospitalization after HSCT), therefore, it is not compulsory for affiliated centers to provide these services and associated medications. Nonetheless, our Institution has made the effort to provide follow-up for up to 1 year (complimentary for the patients) to both, allogeneic and autologous patients affiliated to the SP along with most of the required medications and the NGO *Unidos* is still active. Moreover, the SP does not pay for potential patients' travel expenses associated with the procedure (i.e. meals, ground or air transportation, and lodging). Additionally, the exclusion of financial support for unrelated donors either from the Mexican Registry (DONORMO) or the International Registry (NMDP, National Marrow Donor Program), remains an important barrier for many patients without matched sibling donors requiring an allogeneic HSCT. Another important limitation is that some employed citizens and their dependents, whom are usually affiliated to federal or regional institutions such as the Institute for Social Security and Services for State Workers (ISSSTE) or the Mexican Social Security Institute (IMSS) are banned to access the SP insurance to avoid service overlapping, however, medications for chemotherapy are not widely available even in the previously mentioned governmental institutions and frequently, waiting times are extremely long compared to other centers, for example, our Institution where patients undergo HSCT within a reasonable interval of time, avoiding relapse of the underlying disease or other potential pre-transplant complications.

In conclusion, the *Seguro Popular* has eliminated the patient expense for the hospitalization phase of the procedure which was partially subsidized by our institution with the option to cover the remaining cost by deferred payments, but in at least at our center, it has not improved outcomes. The number of HSCT performed annually have not increased either most likely due to the paucity of improvement and enlargement of infrastructure and health staff by the SP. More importantly, the SP still has deficiencies that must be solved in order to achieve an efficient universal healthcare coverage in Mexico. Further studies should be performed focusing on other expenses; for instance, travel and associated expenditures to potentially highlight that this cost, sometimes, still represents a burden to vulnerable patients undergoing HSCT and even a barrier for some of them, as the population in referral centers is heterogeneous and an important percentage resides in other states, and more importantly, the other centers affiliated to the SP should publish their results for further comparisons as our Institution is the only center that has had aid from a NGO throughout the years.

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