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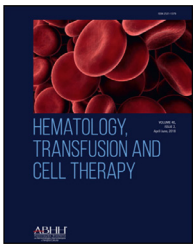

Letter to the Editor

GVHD treatment with extracorporeal photopheresis in Brazil: a national survey

Graft-versus-host disease (GVHD) is a common complication after HCT, impacting on overall survival and quality of life.[1,2] There are few effective treatments for steroid-refractory/dependent acute and chronic GVHD. A treatment option for acute and chronic GVHD is extracorporeal photopheresis (ECP).[3,4] An advantage of ECP is its low toxicity, especially in frail patients and those with uncontrolled infections, in whom systemic immunosuppressive therapy may be deleterious. Nevertheless, ECP shortfalls include requirement of a venous central line in many patients, limited access as it is only available in specialized centers, need for frequent visits, and cost. While in Brazil ECP has been approved by the Brazilian Health Regulatory Agency (ANVISA), the procedure still has to be incorporated by the National Committee for Health Technology Incorporation (CONITEC) into the public system and the National Agency of Supplementary Health (ANS) into the private setting. For this reason, the reimbursement of ECP to health facilities is not mandatory and ultimately depends on the judgment of local hospitals and insurance companies.

To understand the landscape of ECP as second line therapy or beyond for GVHD in Brazil, we sent a survey invitation to HCT centers via the Brazilian Society of Bone Marrow Transplantation and Cell Therapy (SBTMO) in May 2020. The survey was available on the platform *SurveyMonkey* and remained open from May 7th to June 17th, 2020.

Of the 78 centers contacted, 28 responded, corresponding to 27 HCT centers authorized to carry out allogeneic HCT and one ambulatory service that offered treatment with ECP. The 27 transplant centers represented 56% of those performing allogeneic HCTs in 2019.[5] Of the 27 centers,15 were private services. Among the responding centers, 14 of 27 (51%) had performed at least one ECP procedure for GVHD since the beginning of their HCT program. Six of these 14 centers (43%) started using ECP before 2010 while the remaining after 2011. Most procedures took place at services with a volume > 20 allogeneic HCTs/year.

The total number of patients treated with ECP was 215, with 120 (56%) having received this treatment in the last five years. We estimate that this figure represents only 12% of patients (out of 999) requiring second line therapy or beyond for GVHD at the responding centers in the last five years. Approximately, half of the patients were treated at three public academic centers, and 69% were treated with ECP for steroid-refractory/dependent chronic GVHD while the remaining were treated for acute GVHD. Regarding funding sources, the Brazilian public health system (SUS, *Sistema Único de Saúde*) reimbursed 55% of the ECP procedures, while private health insurance companies 37%. The coverage for the cost of ECP treatment was only achieved via litigation in 32% of patients (Figure 1).

Twenty-one of the 27 centers (78%) reported difficulty in performing ECP (more than one may apply): unavailable equipment to deliver ECP (n=12), lack of funding (n=11), unavailable apheresis kits (n=11), lack of expertise (n=2), catheter-related infectious complications (n=1) and distance from the nearest HCT center with ECP (n=1).

By using data from *Associação Brasileira de Transplante de Órgãos* (ABTO),[5] the Brazilian Bone Marrow Transplantation Registry/CIBMTR and the literature,[6,7] we estimate that 895 and 613 patients with acute and chronic GVHD, respectively, required second line therapy or beyond in Brazil from 2015 to 2019. These patients could have potentially benefitted from ECP in case the procedure were more easily available.

This survey shows that ECP has been used in many Brazilian HCT centers for treatment of acute and chronic GVHD despite barriers to equipment/supply acquisition, procedure reimbursement and access. Similar challenges to incorporate ECP into national health systems have been reported in other countries.[8] Most procedures were performed at public health care entities, mainly three academic centers. These centers had a structured long term follow-up service with a considerable number of patients with GVHD and approval of reimbursement of ECP by the local hospital budget. Economic analyses have demonstrated that ECP may deliver greater benefit as second-line therapy for GVHD at a lower cost in a 4 to 5-year timeframe compared to mycophenolate, pentostatin, imatinib, and rituximab.[8,9] These results led to the approval of reimbursement for ECP by health systems in

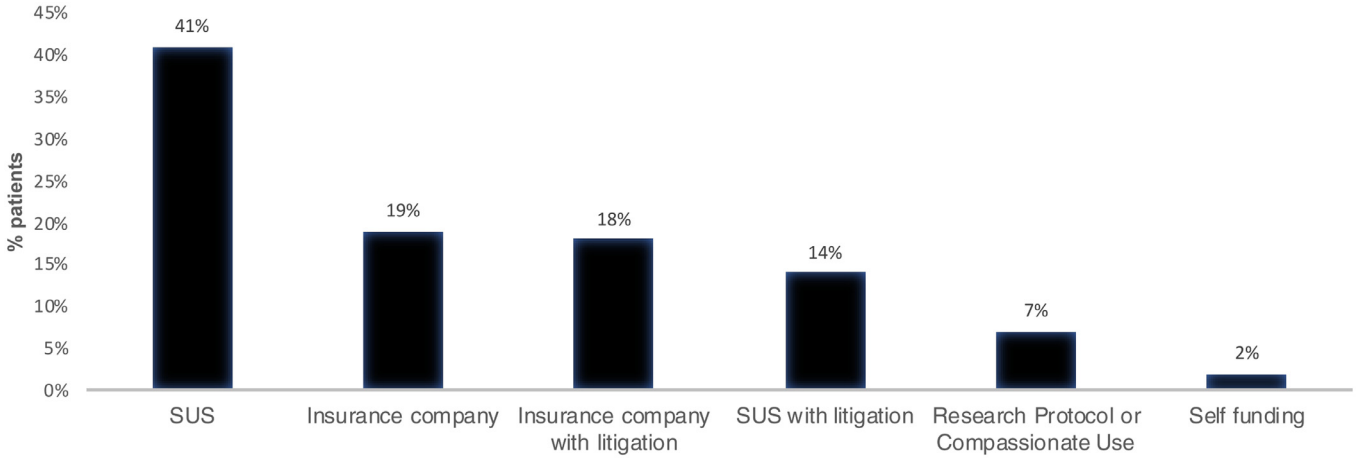

Figure 1 – ECP reimbursement sources
SUS: Sistema Único de Saúde

many countries.[10] However, in Brazil efforts are still needed towards improving access to ECP to treat patients with GVHD by having such a therapy reimbursed in the public and private health systems.

The treatment of steroid-refractory/dependent acute and chronic GVHD has been a dynamic field in recent years. Ibrutinib was the first drug approved by FDA for patients with chronic GVHD failing at least one line of therapy. The approval was based on the results of a phase 1b/2, open-label, multicenter study showing a best overall response rate of 67%.[11] Ruxolitinib has recently emerged as the therapeutic agent for chronic GVHD with best evidence to date based on the phase 3 REACH3 trial (chronic GVHD), showing superior overall responses compared to other standard of care therapies, including ECP.[12] A recent American analysis found ECP was more cost-effective than ruxolitinib and ibrutinib for chronic GVHD.[13] In Brazil, a 6-month estimate of direct costs of ECP to treat an adult patient with chronic GVHD is US$ 50,000 (Therakos^{R} Cellex^{R}, 28 sessions) vs. US$67,200 for ibrutinib (420mg QD) and US$ 35,000 for ruxolitinib (10 mg BID). A formal cost-effectiveness analysis between these therapies is warranted and has to consider indirect costs with personnel, other medical supplies, facility costs and therapy-related complications. Regardless its relative overall efficacy and cost-effectiveness, it is noteworthy to point out that ECP is less immunosuppressive and myelotoxic than other systemic treatments for chronic GVHD, and thus especially interesting for the treatment of patients with active uncontrolled infection, particularly viral, or significant cytopenias. ECP might also prove to be as efficacious or superior to ruxolitinib and ibrutinib for certain involved organs (e.g., skin), which will be better appreciated once the final results of REACH3 (NCT03112603) and iNTEGRATE (NCT02959944) are published.

This report has several limitations. Only a little over half of the active Brazilian centers licensed to perform allogeneic HCT answered the survey, yet nearly all larger centers, which are the ones more likely to offer ECP, are included. The distinction between acute vs. chronic GVHD was not centrally adjudicated, which may lead to inconsistencies. Neither did we have access to individual patient data, preventing further analyses on efficacy and safety of ECP in Brazil.

In conclusion, despite the rapidly changing landscape in the treatment of GVHD, ECP is still an effective therapy for some patients with good level of evidence and may be the only option for frail patients. There are significant hindrances to a wider use of this therapy in Brazil, mainly reimbursement related. We suggest a collaborative effort to generate data about efficacy and cost-effectiveness of ECP for GVHD in Brazil, supporting governmental agencies in making an evidence-based decision on whether the access to this procedure should be expanded.

Conflicts of interest

The authors declare no conflicts of interest.

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Giancarlo Fatobene [a,b,*], Ana Cordeiro [a], Livia Mariano [a,c], Marcia Silva [d], Luis Bouzas [d], Nelson Hamerschlak [e], Maria Cristina Macedo [f], Alessandra Petta [g], Vaneuza Funke [h], Yana Novis [i], Mary E Flowers [j,k,l], Vanderson Rocha [a,b,m],on behalf of the Chronic Graft-versus-Host Disease Brazil-Seattle Consortium Study Group*[a,b,m]

[a] *Laboratorio de Investigação Médica (LIM) 31, Hospital das Clínicas Faculdade de Medicina, Universidade de São Paulo (HCFMUSP), São Paulo, SP, Brazil*
[b] *Hospital Vila Nova Star–Rede D'Or, São Paulo, SP, Brazil*
[c] *Centro Paulista de Oncologia (Oncoclinicas) São Paulo, SP, Brazil*
[d] *Medcel Medicina Celular, Rio de Janeiro, RJ, Brazil*
[e] *Hospital Israelita Albert Einstein, São Paulo, SP, Brazil*
[f] *Hospital 9 de Julho, São Paulo, SP, Brazil*
[g] *Hospital de Amor, Barretos, São Paulo, SP, Brazil*
[h] *Complexo Hospital de Clínicas – Universidade Federal do Paraná HC UFPR), Curitiba, PR, Brazil*
[i] *Hospital Sírio-Libanês, São Paulo, SP, Brazil*
[j] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; USA*
[k] *Seattle Cancer Care Alliance, Seattle, WA, USA*
[l] *University of Washington, Seattle, WA, USA*
[m] *Churchill Hospital, Oxford University Hospitals, Oxford, UK*

*Corresponding author at: Hospital das Clinicas and LIM31, Faculty of Medicine University of São Paulo Av. Dr. Av. Dr. Enéas Carvalho de Aguiar, 155 – 1° andar, 01246-000, São Paulo, SP, Brazil.
E-mail address: gian_fatobene@hotmail.com (G. Fatobene).

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