Development of a Population-Based Cost-Effectiveness Model of Chronic Graft-Versus-Host Disease in Spain

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ABSTRACT

Background: Chronic graft-versus-host disease (cGvHD) is the leading cause of late nonrelapse mortality (transplant-related mortality) after hematopoietic stem cell transplant. Given that there are a wide range of treatment options for cGvHD, assessment of the associated costs and efficacy can help clinicians and health care providers allocate health care resources more efficiently.

Objective: The purpose of this study was to assess the cost-effectiveness of extracorporeal photopheresis (ECP) compared with rituximab (Rmb) and with imatinib (Imt) in patients with cGvHD at 5 years from the perspective of the Spanish National Health System.

Methods: The model assessed the incremental cost-effectiveness/utility ratio of ECP versus Rmb or Imt for 1000 hypothetical patients by using microsimulation cost-effectiveness techniques. Model probabilities were obtained from the literature. Treatment pathways and adverse events were evaluated taking clinical opinion and published reports into consideration. Local data on costs (2010 Euros) and health care resources utilization were validated by the clinical authors. Probabilistic sensitivity analyses were used to assess the robustness of the model.

Results: The greater efficacy of ECP resulted in a gain of 0.011 to 0.024 quality-adjusted life-year in the first year and 0.062 to 0.094 at year 5 compared with Rmb or Imt. The results showed that the higher acquisition cost of ECP versus Imt was compensated for at 9 months by greater efficacy; this higher cost was partially compensated for (€517) by year 5 versus Rmb. After 9 months, ECP was dominant (cheaper and more effective) compared with Imt. The incremental cost-effectiveness ratio of ECP versus Rmb was €29,646 per life-year gained and €24,442 per quality-adjusted life-year gained at year 2.5. Probabilistic sensitivity analysis confirmed the results. The main study limitation was that to assess relative treatment effects, only small studies were available for indirect comparison.

Conclusion: ECP as a third-line therapy for cGvHD is a more cost-effective strategy than Rmb or Imt. (*Clin Ther*. 2012;34:1774–1787) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: chronic graft, host disease, cost-effectiveness, extracorporeal photopheresis.

INTRODUCTION

In Spain, between 2000 and 2500 hematopoietic stem cell transplants are conducted annually, at a maximum rate of 54.14 per million inhabitants, of which 34% are allogeneic.[1] Chronic graft-versus-host disease (cGvHD) is the leading cause of late nonrelapse mortality (transplant-related mortality) after hematopoietic stem cell transplant. It deleteriously affects the quality of life in surviving patients who have otherwise been cured of their underlying disease.[2,3] cGvHD may have debilitating consequences resulting from profound chronic immune suppression that lead to recurrent or life-threatening infections.[4] cGvHD occurs in at least 30% to 50% of recipients of transplants from human leukocyte antigen-matched siblings and in at

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least 60% to 70% of recipients from unrelated donors.[5] A Spanish study found a cumulated incidence of mild, moderate, or severe cGvHD of 29%, 42%, and 28%, respectively, in patients undergoing allogeneic hematopoietic stem cell transplant using peripheral blood from related donors.[6]

The diagnosis and staging working group of the National Institutes of Health Consensus Development Project on cGvHD proposed standard criteria for the diagnosis, organ scoring, and global assessment of cGvHD severity.[2,7] The diagnosis of cGvHD requires the presence of at least 1 clinical diagnostic sign of cGvHD or at least 1 distinctive clinical manifestation confirmed by biopsy or other relevant tests. cGVHD may be restricted to a single organ system, but several organs are usually involved. Clinical features range from edema, erythematous rash, mucositis, diarrhea, and elevated transaminase levels, to more fibrotic and chronic manifestations such as sclerotic, lichen-planus skin changes; fasciitis; Sicca syndrome; joint contractures; esophageal strictures; and bronchiolitis obliterans.[7] The proposed global assessment of severity (mild, moderate, or severe) is derived by combining organ- and site-specific scores.[2,7]

Prednisone, together with a calcineurin inhibitor, is considered the standard regimen for the primary treatment of cGvHD.[8] Although one half of patients respond to first-line treatment, the prognosis of steroid-refractory cGvHD remains poor.[9] There is no standard approach to treat refractory cGvHD, although there are numerous immunosuppressive drugs and other agents available for salvage therapy.

Immunosuppressive treatments that inhibit T-cell activation, proliferation, or survival include mycophenolate mofetil, daclizumab, sirolimus (rapamycin), extracorporeal photopheresis (ECP), and pentostatin (deoxycoformycin).[10] In addition, new strategies such as etanercept, rituximab (Rmb), and imatinib (Imt) have been evaluated.[8,10] However, responses to immunosuppressive drugs are often partial, and patients continue to experience disease symptoms that can significantly impair their quality of life.

ECP is a therapeutic approach based on the biological effect of liquid 8-methoxypsoralen (8-MOP) and ultraviolet light A on mononuclear cells collected by apheresis and reinfused into the patient.[10] This therapy allows treatment using a closed system specifically designed to treat these cells. The liquid 8-MOP eliminates the adverse effects of oral 8-MOP (such as the gastrointestinal adverse effects of psoralen and blood concentration variability in its pharmacokinetics), as well as the need for premedication with this drug and further monitoring of blood levels.[11] ECP, originally developed for the treatment of skin manifestations of cutaneous T-cell lymphoma,[12] has proven effective across a variety of indications, especially acute GvHD and cGvHD in both adult and pediatric patients resistant to standard protocols.[13]

Although T lymphocytes are the therapeutic target of options for the treatment of cGvHD, there is growing evidence regarding the importance of B lymphocytes in the development of the disease. These findings have led to evaluation of the role of Rmb, a chimeric (mouse/human) monoclonal antibody against the protein CD20, in the treatment of cGvHD.[8]

Imt is a potent inhibitor of the tyrosine kinases ABL, platelet-derived growth factor receptor-α and -β, c-KIT, ARG, and LCK. It has proven clinical efficacy in the treatment of the following malignant neoplasms, which are characterized by constitutive activation of these tyrosine kinases: chronic myeloid leukemia, Philadelphia chromosome–positive acute lymphocytic leukemia, dermatofibrosarcoma protuberans, myeloproliferative disorders due to chromosomal rearrangements in the platelet-derived growth factor receptor locus, and gastrointestinal stromal tumors with mutations in c-KIT.[8]

Given that there is a wide range of treatment options for cGvHD, assessment of the associated costs and efficacy can help clinicians and health care providers allocate health care resources more efficiently. Cost-effectiveness analysis is a tool decision makers can use to assess and potentially improve the performance of health systems.[14,15] It indicates which interventions provide the best value for money and enables the interventions which maximize health for the available resources to be chosen. The purpose of the current study was to develop a cost-effectiveness, population-based simulation analysis of cGvHD in Spain that may be used to quantify the future health and economic benefits of ECP versus Rmb or Imt in addition to the usual care of cGvHD after previous treatment failure. Spain is a country with 47 million inhabitants with access to universal public health care free at the point of delivery.

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