

Patients and Methods

Ethics and Included Patients

We included all patients with cGVHD and those who had been treated with ECP in our department between October 2010 and May 2016. Only patients who had received ECP for ≥ 12 months were analyzed retrospectively to assess long-term responses. Skin and mucosal manifestations were diagnosed clinically by dermatologists with a special interest in cGVHD (S.B., M.C.M., C.P., C.B.L.) based upon the distinctive cutaneous or mucosal features of cGVHD. This retrospective study was approved by the Institutional Review Board of CHU Toulouse Hospital (No. 111016) and was carried out in accordance with the Declaration of Helsinki.

ECP Modalities

The decision to start ECP therapy was taken by a multidisciplinary team that included dermatologists and hematologists. An indication for ECP was moderate to severe cGVHD uncontrolled by oral corticosteroids and/or other immunosuppressants. Patients who had a contraindication to immunosuppressants were also treated. ECP contraindications were a total leukocyte count $< 1.0 \times 10^9/L$, intolerance to methoxsalen, heparin or citrate products, hemodynamic instability caused by an ongoing life-threatening infection, or a severe bleeding event.

The ECP equipment used was Uvar XTS[®] and Cellex[®] (Therakos Inc., Mallinckrodt Pharmaceuticals, Mulhuddart, Ireland). The initial frequency of treatment was 2 sessions on 2 consecutive days, every 2 weeks, based on published guidelines [6]. One patient with severe systemic disease (digestive mucosal involvement and contraindication to cyclosporin A because of a DRESS syndrome) started ECP with 1 cycle every week. Three patients started with 1 cycle per month or were given only 1 session a week for practical reasons (geographic distance, professional or personal constraints). As proposed in the guidelines [6], ECP frequency was evaluated every 3 months, and the schedule of ECP was determined according to the assessment. The patients who achieved resolution of all organ involvement and a decrease in the dose of 1 immunosuppressive agent by at least 50% of the initial dosage could reduce the frequency of ECP treatment to every 3 weeks. Every 3 months, if the global clinical and biological examination assessed the absence of relapse, and if the global dose of immunosuppressive agents could have been reduced by 25% more, the frequency of ECP was reduced to every 4, then 6, then 8 weeks. If the dose of immunosuppressive agents was not reduced, the frequency stayed the same for the next 3 months until the next global assessment. If a relapse of

cGVHD of any organ was observed, we returned to the previous schedule. Twelve months after stopping all immunosuppressive treatment without clinical or biological relapse, ECP was stopped.

Evaluation Criteria

Clinical manifestations of cGVHD were evaluated according to their prospectively defined clinical scores at 3-monthly intervals. Modifications to doses and types of immunosuppressant drugs were recorded. A complete response was defined as disappearance of all clinical signs of cGVHD and being able to stop all immunosuppressant drugs without a relapse. Tolerability and adverse effects were documented.

Scores

To evaluate sclerotic lesions in cGVHD, we used a modified version of the Rodnan score (mRodnan), which included the dorsal trunk and included involvement of cGVHD. The highest score possible for mRODNAN is 54 (Figure 2a, as opposed to 51 for the Rodnan score).

Because there is no validated disease severity score for lichen planus [7], we constructed a lichen score to permit a standardized evaluation of cutaneous and mucosal cGVHD lichenoid lesions: we used 4 signs (erythema, infiltration, erosion, reticulation), which were rated between 0 and 4 according to severity, with 4 being the severest. The scores from the 4 signs were summed to evaluate overall severity, with scores ranging from 0 to 16. Extent of disease was evaluated semiquantitatively according to the percentage of skin surface affected, from 0 to 6, and was similar to the PASI score. To calculate the total cGVHD score, the scores from the signs and the skin surface involved were multiplied. The total cGVHD lichen score then varied from 0 to 96 (Fig. 2b).

Data Collection and Analyses

The data were prospectively recorded into standardized medical files. T Software Prism[®], version 5.01 (Graphpad, Irvine, CA, USA), and Excel[®], version 2003–2007 (Microsoft, Redmond, USA) were used for the descriptive analyses. Distributions of the patients' characteristics were expressed as medians and interquartile ranges for continuous variables, and as absolute numbers and percentages for categorical variables. Curves constructed to model changes in skin scores over time were made using Microsoft Excel[®].