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Short Review

Extracorporeal Photopheresis for Non-skin GvHD

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Abstract. *Graft versus host disease (GvHD) is one of the most feared adverse events of allogeneic hematopoietic stem cell transplantation. In severe grades of GvHD patients die from infections due to impairment of their immune defense or therapy-refractory involvement of intestines, liver and lung. Extracorporeal photopheresis is an effective treatment for acute and chronic graft versus host disease without severe impairment of the recipient's immune system. It is generally better known for its effect on skin GvHD but all other manifestations of GvHD can respond as well. Herein we report a brief review of its history and give an overview of the current knowledge of extracorporeal photopheresis in non-skin GvHD.*

History of ECP

Extracorporeal photopheresis (ECP) has come a long way since its invention in 1980. NCBI now lists 1,022 publications on the topic that are rather few compared to other medical interventions. From the idea of PUVA therapy for psoriasis, where the skin is irradiated after ingestion of 8 methoxypsoralen (8-MOP) Richard Edelson and colleagues developed ECP. After leukapheresis 8-MOP is added to the apheresis product and UV irradiation is applied (1). After this, the apheresis product is returned to the patient. This limits the patient's exposure to this photosensitizing 8-MOP and the circulating leukocytes are exposed to a higher dose than in PUVA. This technique was intended to treat cutaneous lymphoma with circulating lymphocytes *e.g.* Sezary`s syndrome (1). Its use has broadened since graft *versus* host disease (GvHD), since allogeneic stem cell transplantation has become a major indication. Its mechanism of action still remains unsolved, however a hypothesis could be that apoptotic lymphocytes after ECP are phagocytosed and presented by monocytes and dendritic cells to CD4 T-cells. This leads to generation of regulatory CD4 T-cells with an immunosuppressive phenotype. This has been shown in mouse models of GvHD and humans with GvHD (2).

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Practice of ECP

ECP has a very good safety profile and very few contraindications. In general the patient should be in a clinical stable situation, so uncontrolled pyrexia, vomiting, diarrhea, hypotonia and anemia with a hematocrit <28%, should be encountered before the procedure can start. It needs a good vascular access, so often shaldon dialysis catheter or dialysis port systems must be used when cubital veins do not suffice. The implantation of these devices has their own complications like arterial puncture and pneumothorax and should be performed by experienced personal. After the procedure patients should wear UV-protective glasses and avoid direct sun exposure due to phototoxic psoralen effects.

GvHD

GvHD after allogeneic stem cell transplantation leads to severe morbidity and mortality among patients transplanted for malignant blood disease. Acute GvHD (aGvHD) summarizes several allo-immune reactions in the stem cell recipient early after transplantation, which include a maculopapular rash (skin-GvH) and fatigue and in more severe forms diarrhea (gastrointestinal GvH) and increased liver enzymes (Liver GvH). Pathophysiology is complex and persistent recipient antigen-presenting cells (APC) are thought to play a major role in presenting allo-antigens to donor lymphocytes introduced with the transplant (3).

Standard treatment is prednisone/prednisolone at 2 mg/kg with good response rates. However steroid-refractory patients with severe aGvHD grade IV have a mortality of 90% (4). Standard second-line treatment for acute GvHD does not exist but broad spectrums of treatment are used, for example rabbit anti-thymocyte globulin. Many patients succumb to infections during such treatment. ECP is attractive for the treatment of acute GvHD as its low toxicity and modest immunosuppressive effect does not substantially increase the patient's risk for infections.

Chronic GvHD (cGvHD) summarizes allo-immune reactions occurring late (>3 months) after transplantation and typically include dry eyes, dry mucous membranes, various dermatological manifestations; bone and joint pain, neuropathy and in the most severe form bronchiolitis obliterans of the lungs (3). Treatment includes steroids and immunosuppressive drugs such as cyclosporine and tacrolimus among many other possible interventions.

GvHD and ECP

Oswianoswki reported a case of extensive cGvHD treated successfully with ECP after failure of steroid and cyclosporine A treatment (5).Well-designed placebo-controlled and adequately powered clinical phase III trials are largely missing in the field of ECP due to various reasons. However the transplant community has adopted this technique and some smaller trials, from which the biggest is the one by Flowers and colleagues (6) and other well-described patient cohorts now define the evidence for use of ECP in GvHD. Several studies have underlined the efficacy of ECP in chronic GvHD, however skin and mucosal involvement responded better than systemic involvement (7). Especially in patients with Bronchiolitis obliterans, ECP had a very limited efficacy (8). The use of ECP for cGvHD has been summarized in recommendations (9).

From the experience of cGvHD, ECP was used to treat acute GvHD with a pilot study in 2000 showing a steroid-sparing effect and responses in grade II-III GvHD, but a very limited effect in severe forms of GvHD (10). A recent meta-analysis underlined that in acute GvHD, ECP is more effective for skin involvement than for systemic manifestations of aGvHD (11). The response rate for skin involvement is 86 % compared to 60% for intestinal GvHD and 68% for liver involvement. From these results one can incorporate this into the management of aGvHD if the technique is readily available for these often acutely sick patients.

Shaughnessy *et al*. incorporated ECP into a myeloablative-conditioning regimen for GvH prevention in 62 patients and demonstrated a disease-free and overall survival benefit to historical controls (12). The incidence of GvHD seemed to be delayed in these patients.

Summary

ECP could be used for all forms of acute and chronic GvHD. Its main indication is steroid-refractory cGvHD, but a broader, even prophylactical use during conditioning can be considered. Its effect is more pronounced in skin GvH than other manifestations of GvH but especially for moderate severity non-skin GvHD, it is worth a try.

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