Transfusion and Apheresis Science xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Mechanistic insights into extracorporeal photochemotherapy: Efficient induction of monocyte-to-dendritic cell maturation

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Photopheresis
Dendritic cells
Antigen-presenting cells
Cancer
Tolerance

ABSTRACT

Extracorporeal photochemotherapy (ECP) is a widely used immunotherapy for cutaneous T cell lymphoma, as well as immunomodulation of graft-versus-host disease (GVHD) and transplanted organ rejection. ECP's mechanism encompasses large-scale physiologic platelet induction of dendritic cells (DCs). The normal bidirectional immunologic talents of DCs likely contribute heavily to ECP's capacity to immunize against tumor antigens, while also suppressing transplant immunopathology. Our understanding of how ECP physiologically induces monocyte-to-DC maturation can enhance the treatment's potency, potentially broaden its use to other cancers and autoimmune disorders and tailor its application to individual patients' diseases. ECP's next decade is filled with promise.

1. Introduction

The Journal's commemoration of this 25th anniversary of the worldwide clinical introduction "Extracorporeal Photochemotherapy" (ECP) offers a special opportunity to reflect on its therapeutic record, as well as the rich promise of its futuristic evolution. ECP's expeditious 1988 FDA approval for cutaneous T cell lymphoma (CTCL) followed our first clinical report [1] of its efficacy by only one year, since advanced CTCL was at that time regularly fatal. When, soon thereafter, the CD8 T cell dependency of its anti-CTCL effects was discovered [2], ECP was identified as the first approved cellular immunotherapy for any cancer.

Since the next FDA-approval for a cellular immunotherapy for a cancer was issued more than two decades later, it was clearly a treatment ahead of its scientific time. Over the intervening years, six prominent features have distinguished it from other immunologic interventions: (1) its beneficial effects as both an immuno-stimulator in a cancer and an immune-modulator in the transplant setting; (2) its unusually advantageous safety profile for a potent therapy; (3) its large scale physiologic induction of antigen presenting cells (APCs), including dendritic cells (DCs); (4) its remarkable clinical specificity for pathogenic T cells; (5) its capacity to extracorporeally sequester and modify processed leukocytes; and (6) its enormous accrual of clinical experience.

ECP's therapeutic impact on tens of thousands of patients, afflicted with cutaneous T cell lymphoma (CTCL) lymphoma, organ transplant rejection and graft-versus-host disease (GVHD), has been thrilling to us all. Sharing that contribution with so many extraordinarily committed and innovative physicians worldwide has been my career highlight.

The story is now in an advanced second stage that offers great amplification of ECP's accomplishments, as the scientific principles underlying its efficacy rapidly crystallize and can now direct the next set of developments. When, in 1982, we first witnessed the initial astonishing response in one my own leukemic CTCL patients, we recognized that ECP had unexpectedly immunized that patient against, and actually eliminated, his malignant T cells.

In the first report of ECP's systemic efficacy, we suggested that, because scientific knowledge existing at that time could not originally explain ECP's clinical effects, its

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1473-0502/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.transci.2013.07.031

Please cite this article in press as: Edelson RL. Mechanistic insights into extracorporeal photochemotherapy: Efficient induction of monocyte-to-dendritic cell maturation. Transf Apheres Sci (2013), http://dx.doi.org/10.1016/j.transci.2013.07.031

underlying mechanism must rely on a previously unrecognized therapeutic principle [1]. We also understood that discovery of that principle would be a challenge that would take the measure of many synergistic researchers and would await a much improved understanding of fundamental immunology itself. The opportunity to weave this perspective, with scenes experienced and lessons learned from that odyssey, offers me a rare chance to tie the storyline that has led to this celebration with predictions of where that immunologic positioning system can now take us.

2. ECP's origin

ECP grew out of my Columbia University research program, which was based on the belief that accruing advances in fundamental T cell biology could be translated into improved treatments for devastating and life-threatening leukemic CTCL. By the conclusion of my fellowship at the National Cancer Institute, we had already shown that CTCL, as a clonal proliferation of malignant skin-homing T cells, is an ideal cancer model for introduction of new immunotherapies [3]. As a neoplastic amplification of skin-homing clonal CD4 T cells, CTCL is readily assessed, both clinically and biologically, since CTCL cells accumulate in the two most accessible tissues, skin and blood. Since its clonotypic T cell receptor (TCR) proteins provide tumor-specific antigens, potential to generate selective anti-CTCL immune clinical responses enticed us.

Because CTCL's clinical manifestations directly reflect the features of the dominant subclone, we initially attempted to exploit that biology to develop effective therapies, leading to multiple transient successes. For example, we found that the leukemic stage of CTCL, typically causing total skin infiltration by malignant T cells (''erythroderma''), could be ameliorated by intensive repetitive leukapheresis [4]. The migratory equilibrium between CTCL cells in the blood and skin compartments was so fluid that aggressive leukapheretic removal of malignant cells, performed essentially on a daily basis over a month, from the blood of a highly leukemic patient, led to parallel diminution of the cutaneous infiltrates and marked reduction of the CTCL cell blood counts. However, those improvements were disappointingly temporary, as new CTCL cell production continued, unimpeded by any immunologic defense. Similarly, we successfully reduced the systemic burden of malignant T cells through intravenous administration of anti-thymocyte globulin [5], but malignant T cell subclones resistant to the anti-T cell antibodies rapidly became dominant and lethal. These early interventions convinced my colleagues and me that, while individual T cell directed therapies had reportable clinical effects, they were merely temporary. As the physicians of these patients, we were not impressed with short-term clinical responses. We needed to find a way to more selectively and persistently suppress, and even eliminate, the malignant CD4 T cells, while leaving the normal T cell compartment, and immunocompetence, largely intact.

With this ambitious goal in mind, we incorporated the phototoxic chemical pyrene into liposomes coated with anti-CD4 monoclonal antibodies [6]. We reasoned that, following CTCL cell binding of these antibody-delivered poison packets, long-wave ultraviolet energy (UVA) activation of the photo-excitable pyrene would selectively kill the malignant T cells. Before administering these liposomes to patients, we fortuitously first tried to enhance the likelihood of lasting clinical impact by extracorporeally reducing the body's load of CTCL cells by a procedure we now call ''ECP''.

To accomplish this cytoreductive preparative step, we conceived a methodology to improve upon the efficiency of leukapheretic preliminary depletion of the body burden of CTCL cells. As indicated above, we already knew that leukemic CTCL cells are in migratory equilibrium with tissue-localized CTCL cells. So, we reasoned that combination of leukapheresis with a different photoactive drug, 8-methoxypsoralen (8-MOP), might markedly enhance the depletion of the body's burden of CTCL cells. That drug naturally occurs in nature in a variety of plant products, including lime and parsnip, is biologically inert unless photoactivated, remains activated for only millionths of a second and, if not bound to nucleic acids and certain proteins, is excreted in virtual entirety within one day. So, 8-MOP is essentially a powerful DNA-active chemotherapeutic agent, which can be turned on by a light switch, directly impacting those cells in the light's path and nowhere else.

We showed that UVA activated 8-MOP (PUVA) cross-links pyrimidine bases of DNA of sister strands, thereby locking shut life-sustaining genes and causing apoptosis of the extracorporeally targeted lymphocytes. By developing monoclonal antibodies specific for these DNA-photoadducts [7], we were able to exquisitely titrate their number and show that, as few as three such cross-links per million DNA base pairs could, with unique gentleness, cause universal lymphocyte apoptosis, while largely sparing the similarly exposed monocytes (6). We now know that this unique capacity to titrate 8-MOP binding to precisely the correct point to open a window between lymphocyte apoptosis and monocyte survival is key to ECP's clinical success, as will be mentioned later in this perspective.

Our intention had been to first demonstrate the safety of this tumor depletion method in five of my own carefully selected leukemic CTCL patients. We therefore started very conservatively with monthly administrations and planned to increase the frequency to daily treatments, until the tumor burden could be maximally reduced, only after initially demonstrating safety. We were quite concerned with the safety of this novel malignant cell depletion method, since it relied on the reticuloendothelial filtration system for removal of the large bolus of intravenously returned dying lymphocytes. We were wary of the possibility of causing ''tumor-lysis syndrome'', precipitated by a systemically overwhelming release of catabolic products of decomposing cancer cells, resulting in hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia, acute uric acid nephropathy, acute kidney failure and commonly death. Fortunately, because of the exceptionally gradual apoptosis caused by 8-MOP, those adverse sequelae have not been encountered by a treatment now known to be remarkably safe.

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