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Combination of photodynamic therapy and immunomodulation — current status and future trends

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Abstract

Photodynamic therapy (PDT) has been used for the treatment of non-malignant and malignant diseases from head to toe. Over the last decade its clinical application has gained increasing acceptance around the world. Pre-clinical studies demonstrate that, in addition to the direct local cytotoxicity and vascular effects, PDT can induce various host immune responses. Recent clinical data also show that improved clinical outcomes are obtained through the combination of PDT and immunomodulation. This review will summarize and discuss recent progress in developing innovative regimen of PDT combined with immunomodulation for the treatment of both non-malignant and malignant diseases.

Keywords

photodynamic therapy; immunomodulation; combination modality

1. INTRODUCTION

Photodynamic therapy (PDT) is a disease site-specific treatment modality. It involves the local or systemic administration of a photosensitizing drug (porphyrin-like, chlorophyll-like or dye compound) followed by irradiating the targeted disease site with non-thermal visible light of appropriate wavelength(s). In the presence of molecular oxygen, the light illumination of photosensitizer and energy transfer can lead to a series of photochemical reactions (Type I and Type II reaction) and generation of various cytotoxic species (e.g. singlet oxygen and other reactive oxygen species), and consequently induce apoptosis and necrosis of targeted cells and tissues.¹ Certain PDT approaches can act on immune cells directly. Immune responses either immunostimulation or immunosuppressive can be elicited during and after PDT. The efficacy of PDT might also be enhanced through effective immunoadjuvants. Several previous reviews have discussed PDT-induced immune responses in animal models, their mechanisms and potential impacts on anti-tumor PDT.^{2–5} The potentials of PDT and immunotherapy combination have been investigated in limited clinical studies. To date, the combination regimen of PDT and immunotherapy has not yet been reviewed elsewhere before. This review article attempts to explore the trend and impact of such combination modality. In this review,

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the modes of PDT applications will be briefly described, immune responses will be summarized and innovative approaches of PDT combined with immunomodulation for the treatment of non-malignant and malignant diseases will be discussed.

2. PHOTODYNAMIC THERAPY

Photodynamic therapy can be performed in various forms in a non-invasive or minimally invasive fashion (Fig 1). The broad spectrum of non-coherent and coherent light sources (e.g. 500 – 800 nm) can match the optimal absorption peak of a specific photosensitizer and a desired tissue penetration depth and therefore offers various treatment options for superficial or interstitial treatment of non-malignant and malignant diseases. A major downside of PDT is the prolonged skin photosensitization and the patient needs to stay away from sunlight exposure for a period of time (1 to 4 weeks). For the majority of patients the light avoidance is tolerable. Over the last decade PDT clinical application has gained increasing acceptance around the world.⁶

A. Cellular-targeted PDT

Conventional cellular-targeted PDT is characterized by a long photosensitizer injection to light irradiation interval (or drug-light interval – DLI), for instance, 24 – 48 hours, to allow target cells to uptake adequate photosensitizer after intravenous administration (IV) of photosensitizer (e.g. Photofrin[®], ALA/PpIX, Foscan[®], Laserphyrin[®]). It has been used primarily for localized superficial or endoluminal malignant and pre-malignant conditions due to their accessibility to the light that can be easily delivered topically or endoscopically. Some photosensitizers and prodrugs (e.g. ALA and its derivatives) can also be applied topically to skin and mucosa lesions or intravesically to the bladder. In which cases, the DLI can be shortened to a few hours. Recently, the progress in light applicator and real-time online monitoring allows PDT application to expand to interstitial treatment of bulky solid tumors.^{6,7}

B. Vascular-targeted PDT

Vascular-targeted PDT is of growing interest and probably by far the most successful PDT application.⁸ It is characterized by a very short DLI, typically 0 – 30 minutes after the completion of IV injection of photosensitizer (e.g. Visudyn[®], Tookad[®]). Under this unique approach, light irradiation takes place while the photosensitizers are still circulating in the vascular compartment and therefore cause direct vascular damages through the low-density lipoprotein receptor-mediated endocytosis pathways and lead to thrombosis and micro-vessel occlusion.⁹ Vascular-targeted PDT has been used primarily for the management of the neovascularization lesion (e.g. wet age-related macular degeneration, AMD) and capillary malformations (e.g. port wine stain birthmarks, PWS).^{10,11} Recently, vascular-targeted PDT has been investigated for curative or palliative treatment of solid tumors (e.g. prostate cancer) by targeting the tumor vasculature.^{12,13} The massive shutdown of pathological and normal vessels can deprive the supply of oxygen and nutrients and subsequently achieve tumor ablation.

C. Extracorporeal PDT

Extracorporeal PDT, commonly known as extracorporeal photophoresis, is a relatively simple *ex vivo* approach which involves a short incubation of the whole blood or blood products with a photosensitizer (e.g. Riboflavin[®], TH9402) and *ex vivo* light irradiation at a shorter wavelength (e.g. 285 – 514 nm). This process may or may not require a photosensitizer extrusion step before and after light irradiation. Extracorporeal PDT has been used for the pathogen reduction in blood transfusion and selective T cells purging in graft-versus-host disease (GvHD) prevention.^{14,15} Noticeably, cross-linking anti-Fas antibody combined with

PDT could have an additive impact against the survival of CD41⁺CD81⁺ thymocytes through proapoptotic pathways.¹⁶ The safety of extracorporeal PDT in the treatment of steroid refractory or intolerant GvHD is currently undergone a formal clinical trial (US Clinical Trial Identifier: NCT00248365).

3. PDT AND IMMUNE RESPONSES

Many pre-clinical studies of various animal models also demonstrate that, in addition to the direct local cellular and vascular effects, PDT can induce host immune responses, which can be either immunostimulation or immunosuppressive. In anti-tumor PDT, the immunostimulation may further enhance the therapeutic effects on the primary tumor as well as metastasis.^{4,5,17,18} Recent findings suggest that PDT-induced strong local inflammatory and cellular reactions may be an initiating factor for activating the host immunity. During and after PDT, pro-inflammatory damages formed in cellular membranes and the blood vessel walls of treated site start to recruit dendritic cells (DCs), neutrophils, mast cells, monocytes and macrophages. These cells can also release more inflammatory mediators to enable massive recruitment of immune cells (e.g. CD4⁺, CD8⁺, and CD68⁺ T cells) to PDT-treated site.^{19,20} Some cellular factors, such as heat-shock protein 70 (HSP70), may be involved in interacting with antigen-presenting cells (APCs) and stimulate anti-tumor immune responses.^{21,22} PDT can also activate the expression and production of several cytokines and chemokines, such as IL-1 β , IL-2, IL-6, IL-8, IL-10, IFN- γ , TNF- α , and G-CSF. A recent clinical study examined serum cytokine levels in cancer patients who underwent adjuvant PDT and showed an elevated level of IL-1 β , IL-6, IL-8, and IL-10.²³ Although the examination of host immune responses (e.g. pre- and post-PDT biopsies) has rarely been enforced in routine clinical practice, it is well-known that some of these cytokines could play important roles in regulating host immune response involving both lymphoid and non-lymphoid cells.

The extensive involvement of cytokines in PDT-induced immune response leads to an attempt to optimize PDT efficacy through the modulation of important inflammatory and immune mediators. The activation of a specific and systemic host immune response may result in not only further destruction of remaining local tumor cells but also the prevention of possible recurrence and metastasis. Therefore, PDT-induced antitumor immune response might play an important rule in successful control of malignant diseases, at least in animal models.^{24–28} Furthermore, the antitumor efficacy of PDT might be enhanced through an effective immunoadjuvant to further expand its usefulness for a possible control of distant metastasis and recurrence. Preclinical studies also show that the combination of PDT with intratumoral injection of DCs, CpG-oligodeoxynucleotide (CpG-ODNs) and/or PDT-cell lysates produced effective synergistic response by activating innate and adaptive antitumor immunity.^{29–31} PDT-generated tumor cell lysates can be potent vaccines and more effective than other modes of creating whole tumor vaccines.³² Nanoparticle-based delivery complex might facilitate drug delivery and enhance overall effectiveness.^{33,34} Nevertheless, one must also recognize that, in clinical practice, the optimal PDT regimen for achieving tumor ablation might be different from the optimal PDT regimen for producing immune response.^{5,35} A combination modality with the second regimen of mechanistically nonoverlapping or overlapping immunotherapy, is an attractive option.^{36,37} Such treatment protocols merit further clinical investigation.

4. COMBINATION OF PDT AND IMMUNOMODULATION IN CLINICAL TRIALS

Amongst the approved and suggested PDT indications, immunological factors are involved not only in the pathogenesis of these diseases, but also in their treatment. More clinical data indicated that improved clinical outcomes could be obtained in the combination of PDT and immunomodulation approaches for both non-malignant and malignant diseases. The following

sections will highlight recent progress in developing innovative clinical approaches of PDT combined with immunomodulation for the treatment of eye and skin diseases.

A. Combined PDT with triamcinolone for choroidal neovascularization

Although verteporfin (benzoporphyrin derivative monoacid ring A, BPD-MA) was synthesized in the mid-1980s with an intention of cancer treatment, it has been used primarily for ocular PDT.³⁸ PDT with verteporfin (also known as PDT-V) has been approved worldwide since 2000 as a first-line therapy for the treatment of patients with predominantly classic subfoveal choroidal neovascularization (CNV) due to AMD, pathologic myopia or presumed ocular histoplasmosis. In the western world, AMD is one of the leading causes of blindness due to the formation of the subfoveal CNV. PDT with verteporfin and laser photocoagulation are the only proven therapies for the subfoveal CNV. PDT with verteporfin has to be carried out while the photosensitizer is in the general circulation in order to maximize anti-vascular effect and ultimately to achieve complete occlusion of CNV lesions, stabilize leakage and gain visual acuity or limit visual loss.⁹ The typical ocular PDT regimen includes (i) IV infusing Visudyne® (verteporfin for injection, Novartis) at 6 mg/m² of body surface area for 10 minutes and (ii) irradiating with a laser light of 689 nm through an ophthalmoscope at an intensity of 600 mW/cm² for 83 seconds at 5 minutes after the completion of the drug infusion (i.e. at the 15th minute after the onset of drug infusion). A total light dose of 50 J/cm² is delivered to a spot or disc size with a diameter 1 mm larger than the greatest linear dimension of the CNV lesion. At follow-up examinations every 3 months, re-treatment with the same regimen shall be applied if the angiograph shows fluorescein leakage.⁹

CNV eyes often show the histopathologic evidence of inflammation and other immunological changes. Examination of CNV complexes has shown the presence of inflammatory cells. The inflammatory cells may play a role in neovascularization in the subretinal space. There is a body of clinical evidences suggesting that the intravitreal injection of steroids may have a beneficial effect for CNV patients.³⁹ Nonetheless, PDT-induced inflammatory reactions are two sides of the same coin. The acute inflammatory response might cause a transient visual disturbance and the proliferation of vessels might cause treatment failure.^{40,41} Anti-inflammatory adjuvant therapy might have the potential to counteract some of these adverse effects (Fig. 2).⁴²

Triamcinolone acetonide is a synthetic glucocorticoid, a class of potent anti-inflammatory/immunosuppressive drugs that has been shown to inhibit cellular proliferation and new vessel growth *in vitro* and *in vivo*. Intravitreal triamcinolone acetonide (IVTA) has been shown to inhibit retinal neovascularization in experimental animal models and to reduce the breakdown of the blood–retinal barrier, a pathologic mechanism related to visual loss. Corticosteroids can inhibit the arachidonic acid pathway which leads to the production of prostaglandins, known to be important mediators of vascular permeability. They also down-regulate the production of vascular endothelial growth factor (VEGF), a potent stimulator of new vessel growth and vascular permeability. Several clinical studies have shown that triamcinolone appears to have a favorable effect on visual acuity and fundus appearance. Intravitreal injection of triamcinolone can enhance anti-angiogenetic and anti-edematous effects and therefore theoretically may be an ideal adjunct therapy for CNV in combination with PDT.

Although intravitreal injection of triamcinolone alone in treating CVN secondary to AMD might not benefit visual outcome, clinical studies demonstrate that intravitreal triamcinolone therapy has a synergistic and long-lasting anti-angiogenic effect if used in combination with PDT.^{43,44} In such a case, steroid-induced local immune suppression and PDT induced local immune response might interact with each other in the subretinal space. Those interactions and balances might be a key factor to mediate and control inflammatory reactions and therefore the final clinical outcome. Administration of IVTA (e.g. Kenacort-A at 40 mg/ml) in the peri-

PDT period has been demonstrated to enhance the effectiveness of PDT and reduce the frequency and duration of treatment.⁴⁵ It has been estimated that nowadays more than 70% of all cases of PDT with verteporfin for exudative macular degeneration are combined with intravitreal triamcinolone injection although the optimal sequence, timing, and dose have not yet been established. The synergistic effect of ocular PDT and intravitreal steroid therapy certainly deserves further study.

Noticeably, the amount of VEGF, the major cytokines involved in initiating angiogenesis, has been shown to be proportional to the amount of inflammatory cells present prior to or post PDT. It is not a surprise that the combination of verteporfin PDT and intravitreal injection of a monoclonal antibody against VEGF can significantly improve the best-corrected visual acuity.⁴⁶ Stimulated by the regulatory approval of anti-VEGF agents Avastin (bevacizumab - a monoclonal antibody against VEGF), Lucentis (ranibizumab - a monoclonal antibody fragment derived from the same parent murine antibody as bevacizumab), and Vatalanib (PTK787- a small molecule tyrosine kinase inhibitor which can selectively block VEGF receptor 2), one can expect the growing trend of combination strategies of PDT and anti-VEGF signaling at this anti-VEGF era. Several clinical trials have been initiated to test the safety and efficacy of the combination of PDT and anti-VEGF agents. For example: PDT-V + Avastin (Clinical Trial Identifiers: NCT00347399, 00359164, 00376701, and 00451763), PDT-V + Lucentis (Clinical Trial Identifiers: NCT00433017, 00436553, 00455871, and 00492284) or PDT-V + Vatalanib (Clinical Trial Identifier: NCT00138632). Possible advantages of combination modality include reducing PDT light fluence rate or drug dose, delaying time to retreatment and reducing the average number of repeated treatment and overall cost. Soon the triple therapy of PDT, anti-VEGF and steroids (e.g. dexamethasone) can be seen on the horizon (Clinical Trial Identifiers: NCT00390208 and 00492284).⁴⁷

B. Combined PDT with imiquimod for pre-malignant and malignant skin diseases

Several types of dermatologic conditions were among the first to be studied due to their accessibility to topical application of photosensitizer and external light.⁶ Thomas Dougherty *et al.* studied skin PDT in the 1970s using hemotoporphyrin derivative (HpD) and a xenon arc lamp in patients who suffered primary or secondary skin cancers. This pioneer study demonstrated that the primary skin cancers that showed a complete response (CR) included squamous cell carcinomas (SCCs, 20%), basal cell carcinomas (BCCs, 70–80%) and malignant melanomas (50%), and the secondary cancers originated from primary breast cancer, colon cancer and endometrium cancer (80%).⁴⁸ Interstitial PDT might be an option for subcutaneous and cutaneous tumors of a larger volume.

Since the discovery of endogenous protoporphyrin IX (PpIX) photosensitization induced by exogenous administration of prodrug 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MLA), skin pre-malignant and malignant lesions also became a favorite target of topical PDT with the exception of the pigmented melanomas due to a limited light penetration. However, a recent clinical investigation indicates that a combination of photothermal therapy and imiquimod (an immune response modifier, see below) may be useful for difficult-to-manage diseases such as melanoma.⁴⁹ Photothermal and immunological combination may be more effective in immunological stimulation due to its mechanism of large scale tumor destruction and partial denature of tumor protein. Nevertheless, an active immunological stimulation is needed to augment the efficacy of phototherapy.¹⁸

Imiquimod, a topically applied imidazoquinoline immunomodulator, is a potent stimulator of both the innate immune response and the cellular arm of acquired immunity. Imiquimod activates cells of the innate immune system (e.g. monocytes, macrophages, and dendritic cells) by binding to Toll-like receptor 7 and 8 (TLR-7, TLR-8) on the cell surfaces. This results in the NF-kappaB-dependent release of proinflammatory cytokines (e.g. IFN- α , TNF- α , IL-12)

and chemokines (e.g. IL1, IL6, IL8, and IL10). Some of the cytokines also enhance the acquired immunity, including the activation of T-helper cell type 1 and other cell-mediated immune responses that help control viruses, tumors, and intracellular parasites.^{50,51} Imiquimod-mediated production of INF- γ and IL18 has also a strong inhibitive effect on tumor cell-induced angiogenesis.⁵² Imiquimod was the first FDA-approved immune response modifier for the treatment of external genital and perianal warts in 1997. Since then, its antiviral and anti-tumor properties have been used in the treatment of a variety of dermatologic conditions. Several ongoing clinical trials indicate that Imiquimod 5% cream (Aldara[®] Cream) appears to have a favorable effect on actinic keratosis (AK), superficial BCCs and SCCs, and malignant melanomas.

Actinic keratosis, a pre-malignant lesion became the first approved dermatologic indication of ALA-PDT in the early 2000's. Recently, Levulan[®] and Metvix[®] have been approved for AK in several countries. Clinical investigations of topical PDT have also been extended to BCCs, basaloid follicular hamartomas, SCC *in situ* (Bowen's disease), cutaneous T-cell lymphoma, and sebaceous gland hyperplasia in recent years. PDT may be useful for both Mediterranean and HIV-related Kaposi's sarcomas since it can be repeated and will not cause immunosuppression. Recent clinical data also suggests that PDT might be useful for the treatment of the pigmented melanomas although in general PDT is considered unsuitable for the pigmented lesion due to a limited light penetration. Although comparison studies have been reported for the evaluation of PDT and imiquimod immunomodulation for certain types of skin cancers,⁵³ it has not yet been confirmed whether the combination of PDT and imiquimod could further enhance the overall cure rate. Because of a growing understanding of the immune mechanisms within the skin, the opportunity has arisen to assist the body's immune system to effectively treat dermatologic conditions. Nevertheless, since PDT and imiquimod share the same indications and immunomodulation pathways (Fig. 3), such as stimulating a cutaneous immune response characterized by increasing in the activated dendritic cells and CD4⁺ and CD8⁺ T cells, it appears that such combination underlies the great utility of PDT and imiquimod for treating invasive skin cancers. The definitive roles of the combination of PDT and imiquimod immunotherapy in dermatology need to be determined in controlled trials.⁵⁴

Bowenoid papulosis (BP) is a pre-malignant condition affecting the ano-genital area. Pathogenesis may be associated with high-risk human papillomavirus (HPV) genotypes, and sexual transmission is the most likely mode of acquisition. The treatment of BP remains to be controversial, since the nature of BP lesions is still not completely understood and relapse often occurs. However, with increasing incidence in the younger population, two primary objectives are mandatory for the management of BP: (i) the prevention of invasive vulvar cancer and (ii) the preservation of the normal tissue and function.⁵⁵ Several case reports suggest that topical application of imiquimod might be effective in inactivating HPV and treating BP.^{56–59} Recent clinical data indicates that the combined modality of multiple sessions of imiquimod (4 weeks) and ALA-PDT (1–4 times) is tolerable, effective and associated with a low incidence of recurrence.⁶⁰

C. Antibody-directed PDT

In addition to the combination with a variety of immunomodulation, there are several other potential immunological approaches that might enhance PDT efficacy through different mechanisms and pathways. This section will focus on antibody-directed PDT.

One limitation of anti-tumor PDT, however, is the lack of tumor selectivity of the photosensitizers, which often has been overcriticized. Enhancing selectivity may be achieved by attempting to increase both the photosensitizer concentration to the target cancerous cells and the selectivity between the target and surrounding normal tissue. One of the immunological

approaches for these purposes is the development of target-specific modality using photosensitizer immunoconjugates (PIC).^{61,62}

Interestingly, the term “photoimmunotherapy” was first used to describe the tumor-specific antibody-directed PDT in the middle 1980s.⁶³ Target-specific PDT, targeted PDT, photoimmunotherapy (PIT) or antibody-directed PDT uses the immuno-conjugated photosensitizers which can combine the specificity of a monoclonal antibody (MAb) to an overexpressed cellular marker with the phototoxic properties of the conjugated PDT photosensitizer. The targeted cellular marker can be a tumor-associated or non-tumor-associated marker. The antibody conjugation may or may not necessarily enhance the process of internalization, although the internalization might enhance PDT-induced cytotoxicity.^{64,65}

Both *in-vitro* and *in vivo* experimental studies have demonstrated that antibody-directed PDT may be useful for the treatment of non-malignant and malignant diseases. Recent data demonstrate that high-quality PIC might be developed by adding an isothiocyanate group to porphyrins, and the use of internalizing MAb could significantly increase the photodynamic efficiency of PIC in animal tumor models.⁶⁶ As described above, VEGF plays a role in the pathogenesis of AMD and therefore it might be a potential target of antibody-directed PDT. A recent experimental study showed that the conjugation of verteporfin to anti-VEGF antibody was possible without the loss of its photosensitizing properties.⁶⁷ The list of antigen targets and MAb candidates is still expanding, which includes but is not limited to carcinoembryonic antigen, CD20 antigen (e.g. rituximab), epidermal growth factor receptor (EGFR), HER-2, ILs, and tumour-specific scFv fragment.^{68–75} It is true that despite the encouraging progress made in basic research over the past two decades, showing the high selectivity of photoimmunoconjugates and improvement of PDT efficacy, antibody-directed PDT still awaits initial clinical evaluation.⁷⁶

The importance of antibiotic resistance in medical practice is increasing. An alternative approach may be to use PDT.⁷⁷ Early studies have demonstrated that methicillin-resistant *Staphylococcus aureus* (MRSA) can be killed with an immuno-globulin G (IgG)-tin(IV)-Chlorin e6 (SnCe6) conjugate and red light although the effectiveness was weak. In an effort to improve the effectiveness, an antibody raised against MRSA was used to make an antibody-SnCe6 conjugate which was capable of targeting many MRSA strains in all growth phases.⁷⁸ Unfortunately, clinical use of these new combination modalities is limited due to the lack of well-characterized human antibody and PIC.

5. FUTURE PROSPECTS

Evidences are now accumulating that amongst the approved and suggested PDT indications, immunological factors are involved not only in the pathogenesis of these diseases, but also in their treatment. Pre-clinical studies of immunological approaches to enhance PDT efficacy are still very active around the world. More clinical data indicate that improved clinical outcomes are seen in the combined modality approaches involving immunotherapy and PDT for both non-malignant and malignant diseases. But clinical use of these new combination modalities is limited due to various reasons – mainly lack of enthusiasm perhaps. Nonetheless, the extended experience learnt from current trials of combination regimen of PDT and anti-VEGF therapy in the treatment of choroidal neovascularization might fundamentally change the perspectives on the vascular-targeted PDT. The vascular-targeted PDT is a promising option in the treatment of cutaneous vascular lesion such as PWS birthmarks,⁷⁹ but re-emergence tends to occur in some PWS patients though it is not clear whether or not the neovascularization plays roles in recurrent and refractory PWS. Growing evidence of preclinical studies suggests that both vascular-and cellular-targeted PDT can trigger the neovascularization in solid tumors.

Therefore, combined modality approaches, such as PDT and anti-VEGF therapy, might provide a better means to target both the tumor itself and its microenvironment.^{80,81}

It is true that there probably is no field in medicine that has provided as much hope, or as much disappointment, as the field of immunotherapy. The human immune system is extremely complex and highly specific. In each individual, the relationship between the immune system and disease is unique and, by nature, this makes immunotherapy studies complicated and therefore difficult to conduct. Furthermore, the human immune system compromises a variety of cell types whose activities must be carefully regulated to act as a coherent unit in host defense.⁸² Many of the immunological approaches developed in other species may not be predictive of the effectiveness of these approaches in humans.⁸³ Inevitably, PDT faces the same phenomenon.⁵ Although many problems and challenges remain, promising results in preclinical and clinical settings have been seen in PDT and immune manipulation. New progress in the combination regimen of PDT and immunotherapy will need the strengthening of current clinical studies and the gathering of a large quantity of clinical data from patients undergoing combination therapies.

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Figure 1.

Conventional form of photodynamic therapy. The drug to light interval (DLI) in PDT is a determining factor of the mode of action. At short DLI (< 30 min), the light irradiation takes place while the photosensitizers (ps) are still circulating in the vascular compartment and therefore mainly causes direct vascular damages. Long DLI (> 24 h) allows the photosensitizers to be accumulated by target cells and therefore causes intracellular damages.

Figure 2.

The “Ying-Yang” action of photodynamic therapy and triamcinolone. Some adverse effects, such as acute inflammatory response and vessel proliferation, are associated with PDT and responsible for the transient visual disturbance and treatment failure. Intravitreal injection of triamcinolone, an anti-inflammatory agent, may counteract these adverse effects and improve clinical outcomes.

Figure 3.

The synergistic action of photodynamic therapy and imiquimod. Imiquimod shares the same immunomodulation pathways with PDT in enhancing the acquired anti-tumor immunity. PDT can activate monocytes (M), macrophages (M), mast (M), neutrophils (N) and dendritic cells (DC). Imiquimod can also activate the dendritic cells by binding to Toll-like receptor 7 and 8 (TLR-7 and TLR-8) on the cell surface and release proinflammatory cytokines (e.g. IFN- α , TNF- α , IL-12), and activate CD4⁺ and CD8⁺ T cells (T).