

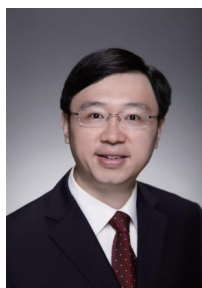
重点选题“皮肤病诊疗”·专题专栏

光动力治疗在皮肤疾病领域的研究进展[▲]

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【提要】 随着科学技术的进步,光动力治疗逐渐在临床上被广泛应用,并在皮肤疾病领域取得显著成效。光动力治疗在肿瘤性皮肤病、感染性皮肤病等多种皮肤病治疗中的有效性、安全性均不亚于传统治疗手段,但仍有其局限性。本文结合近期研究进展,介绍光动力治疗的原理,光动力治疗在肿瘤性皮肤病、感染性皮肤病及其他皮肤疾病领域的具体应用,并总结光动力治疗在皮肤疾病领域面临的挑战与未来研究方向,以期光动力治疗的临床应用提供新的视角。

【关键词】 光动力治疗;皮肤疾病;综述

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Research progress on photodynamics therapy in the field of skin diseases

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【Abstract】 With the development of science and technology, photodynamic therapy has been widely used in clinical practice and has achieved remarkable results in the field of skin diseases. The effectiveness and safety of photodynamic therapy in the treatment of neoplastic skin diseases, infectious skin diseases and other skin diseases are not inferior to traditional treatment methods, but it still has its limitations. Based on the recent research progress, this paper introduces the principle of photodynamic therapy, the specific application to the fields of photodynamic therapy in neoplastic skin diseases, infectious skin diseases and other skin diseases, and summarizes the challenges and future research directions of photodynamic therapy in the field of skin diseases, so as to provide a new perspective for the clinical application of photodynamic therapy.

【Key words】 Photodynamic therapy, Skin diseases, Review

皮肤是人体最大的器官,其病变不仅影响正常的生物学功能,导致瘙痒、疼痛等不适,若发生在暴露部位还会影响美观与身心健康。不同类型的皮肤疾病往往采取不同的治疗手段。例如,对于可切除的皮肤肿瘤,应及时行外科手术切除;对于皮肤真菌感染,应及时口服或外用抗真菌药。然而,手术切口可能因张力大而形成瘢痕,抗真菌药物可能具有肝肾毒性或产生耐药性。这些治疗的不足使得光动力治疗(photodynamic therapy, PDT)等新型治疗手段逐渐受到关注。

PDT是通过光敏剂与氧气在光照条件下发生反应进行的治疗策略,其作用已在肿瘤治疗领域得到证实。近年来,研究者发现PDT可应用于皮肤疾病的治疗,包括肿瘤性皮肤疾病、感染性皮肤疾病、炎症性皮肤疾病等。例如,PDT产生的单线态氧不仅可以通过直接杀伤肿瘤细胞来治疗皮肤肿瘤,还能够抑制皮脂腺细胞活动,从而调节痤疮部位的局部免疫与炎症反应等^[1]。大量的临床研究与荟萃分析为PDT适应证的拓展提供了充分的证据,部分已总结形成专家指南或共识,但不同皮肤疾病的具体治疗参数、适用人群及可能发生的副作用仍需进一步探讨^[2]。因此,回顾现阶段PDT在皮肤疾病中应用的研究进展,有助于总结已取得的研究成果,为后续的研究计划提供思路。本文旨在总结近期PDT在皮肤疾病领域的研究进展,包括以下内容:PDT的原理;PDT在皮肤疾病中的具体应用,包括肿瘤性皮肤疾病、感染性皮肤疾病等;PDT在皮肤疾病领域的挑战及机遇。

1 PDT的原理

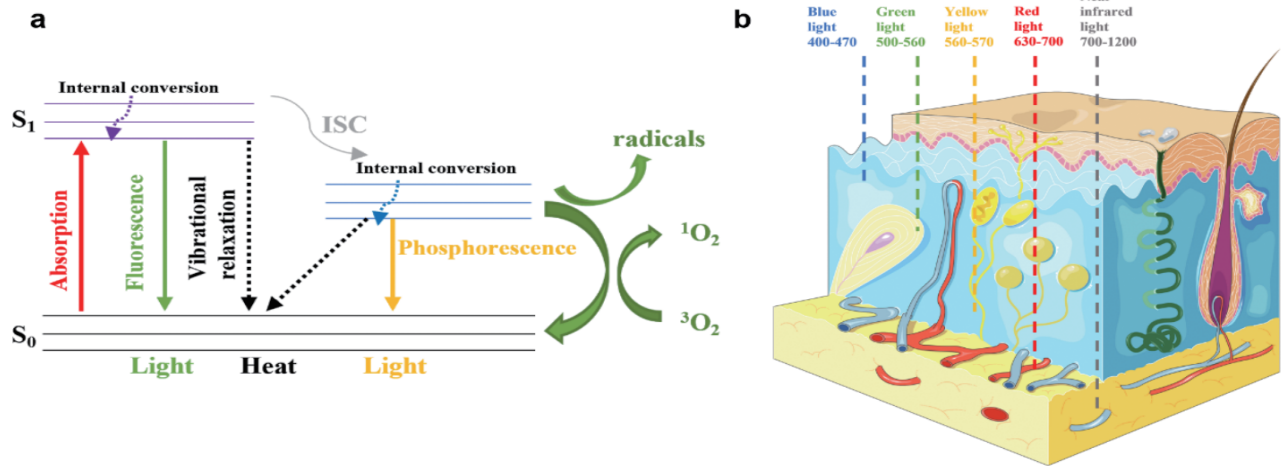
PDT,即通过特定波长的光激发光敏剂消耗氧气从而产生活性氧簇(reactive oxygen species, ROS)的

治疗模式,具有高选择性、非侵入性、可重复性等特点(图1a)^[3-4]。PDT具有独特的优势:一方面,光敏剂在暗光下毒性低或无毒,而在光照条件下能产生大量ROS,具有良好的选择性;另一方面,光线可以被调谐和聚焦,从而实现精准治疗,因此可减少对健康组织的损害。更重要的是,由于光穿透组织的能力有限,ROS的作用范围主要在其产生部位,因此PDT尤其适合用于皮肤疾病的治疗,避免了PDT应用于内脏病变时需要依赖内窥镜光源的不足。

PDT的三要素是光源、氧气与光敏剂^[5]。光源的波长须依据光敏剂的吸收峰进行选择。此外,不同波长的光源具有不同程度的穿透能力(图1b)。PDT常用激发光源有红光(约635 nm)和蓝光(约410 nm),常用的光源发射器有氩氦激光器、半导体激光器、发光二极管等,日光等亦可作为激发光源。蓝光的穿透能力较弱,而红光的穿透能力较强,其中近红外光可穿透至真皮组织区域,最大深度达1 cm。日光是复合光,可在多个波长持续激活光动力反应,可缩短就医时间,减轻疼痛等,但受气候、地理因素及发病部位影响^[6]。氧气是PDT产生ROS的原料之一,但体内实质性肿瘤组织往往呈乏氧状态,这影响了PDT的治疗效果^[7]。而皮肤组织与外界接触,PDT过程可直接消耗空气中的氧气,这成为其应用于皮肤疾病领域的优势。光敏剂可分为第一代光敏剂与第二代光敏剂,第一代光敏剂为血卟啉衍生物类,可用于治疗皮肤肿瘤。然而,第一代光敏剂的纯度低、组织敏感性和特异性差等缺陷阻碍了其进一步应用。在此基础上改进并衍生了第二代光敏剂,如5-氨基酮戊酸(5-aminolevulinic acid, ALA)及氨基乙酰丙酸甲酯(methyl aminolevulinate, MAL)等,在临床上得到了广泛应用。ALA与MAL可在肿瘤组织内积累并通过细胞内血红素生物合成途径转化为原卟啉IX,进而发

挥治疗作用^[8]。为了进一步提高组织靶向性并避免全身毒性作用,第三代光敏剂在第二代光敏剂的基

础上增加偶联抗体或配体等,但目前其仍未进入大规模临床试验。



注:(a)光敏药物在吸收能量后从基态(S_0)跃迁至激发态(S_1),并在回到基态的过程中利用多种途径将能量加以转化,产生单线态氧。Light、Heat分别指光和热,Absorption指吸收,Fluorescence指荧光,Phosphorescence指磷光,Internal conversion指内部能量转换,ISC指系间窜越,radicals指自由基, 1O_2 指单线态氧自由基, 3O_2 指三线态氧。(b)不同波长光源的穿透能力示意图(波长单位:nm)。Blue light、Green light、Yellow light、Red light、Near infrared light分别指蓝光、绿光、黄光、红光、近红外光。

图1 PDT的原理

2 PDT在肿瘤性皮肤病疾病领域中的应用

随着科学技术的发展,PDT已经在多种疾病尤其是皮肤疾病的临床治疗上得到应用,并取得肯定的疗效^[9]。PDT在皮肤基底细胞癌(basal cell carcinoma, BCC)、鳞状细胞癌(squamous cell carcinoma, SCC)等肿瘤性皮肤病治疗中的有效性已得到大量循证医学证据证实,且已有多项相关指南与专家共识发布。

BCC是常见的皮肤肿瘤之一。手术是皮肤BCC最常见的治疗方式,但手术后可能形成瘢痕,影响美观。PDT具有患者依从性好和美容效果良好等优点,因此被广泛应用于皮肤BCC的治疗^[10]。浅表型BCC及深度<2 mm的结节性BCC的皮损组织厚度较薄,有助于光照和光敏剂穿透,因此PDT效果与手术治疗相当(清除率分别为92%、99%,1年复发率分别为9%、0),且美容效果更优(推荐等级A级)^[11-12]。此外,手术联合PDT治疗可提升疗效,若皮损面积较大,可先进行PDT再进行手术治疗,以减少手术切除面积^[13-14]。

鲍温病是一种仅局限于表皮的皮肤原位SCC,高发于高龄人群及日晒部位。ALA-PDT可用于无法耐受手术或因美观、功能原因拒绝手术的病例(推荐等级为A级)^[1,10]。在面部等影响美观的部位,PDT所致的瘢痕较小,其应用于鲍温病时可获得满意的疗效及美容效果^[15]。PDT对鲍温病的清除率与皮损直径、生长部位和孵育时间相关,对皮损直径<2 cm、皮损位于面部且ALA孵育时间>4 h者疗效更好^[16]。值得注意的是,在应用PDT前,应排除疾病转移及侵

袭性SCC。

日光角化病(solar keratosis, SK)是一种癌前病变,表现为聚集在表皮的角化细胞发育不良,有可能演变为SCC。SK的发病原因与长期的紫外线暴露相关,易发生在阳光暴露部位,表现为红色或褐色斑块,带来压痛、瘙痒、出血及美容问题^[17]。PDT可应用于SK的治疗,其完全缓解率高于其他疗法,且其复发率与其他疗法相比差异无统计学意义^[18]。然而,PDT的不良事件发生率较高,包括红斑、烧灼感、瘙痒、水疱等,但与其他疗法相比差异无统计学意义^[19]。

皮肤T细胞淋巴瘤是一种罕见的非霍奇金淋巴瘤,临床表现多样,包括破溃、斑块、红皮病样表现等^[20]。目前,多种治疗方案因各种不足而在皮肤T细胞淋巴瘤中的应用受限,例如,局部化疗可导致接触性皮炎,放疗可导致脱发,咪喹莫特可导致局部炎症等^[21]。由于皮肤T细胞淋巴瘤的病情呈慢性进展,治疗的短期耐受性与长期安全性是制定该病治疗方案时的重要考虑因素^[22]。一项纳入169例皮肤T细胞淋巴瘤患者的Ⅲ期临床试验表明,基于金丝桃素的PDT对皮肤T细胞淋巴瘤的斑块病变具有良好的短期和长期安全性,可作为无法耐受一线治疗患者的补充治疗^[23]。

乳房外Paget病(extramammary Paget's disease, EMPD)是一种罕见的上皮恶性肿瘤,发生于顶泌汗腺丰富的皮肤,临床表现包括红斑、瘙痒、斑块等,首选手术治疗^[24]。对于无法手术的患者,PDT可缩小病灶大小并减轻症状^[25]。一项系统评价结果显示,单纯ALA-PDT

与 MAL-PDT 在 EMPD 中的完全缓解率分别为 57.7% 与 27.4%, 复发率分别为 40.0% 与 35.0%, 而 PDT 联合咪喹莫特、激光治疗的完全缓解率分别为 100.0%、60.0%, 复发率分别为 0、8.3%^[26]。另有研究结果显示, 作为联合疗法, MAL-PDT 联合咪喹莫特可在发病 2 年内持续控制肛周 EMPD 的发展^[27]。另外, 光动力诊断可用于手术切缘评估。Li 等^[28]采用基于光动力诊断的肿瘤切除与 PDT 联合治疗 EMPD 患者, 所有患者在随访时间(平均 2.9 年)内无复发。

此外, 由于 PDT 可有效减小多种皮肤肿瘤体积并减轻并发症, 其作为潜在的新辅助治疗手段逐渐受到关注。在部分瘤体体积过大、侵袭性或多发性、美容或功能敏感部位的肿瘤性皮肤疾病中, PDT 作为新辅助疗法取得了显著成效。一项前瞻性研究结果显示, 33 例皮肤 BCC 患者接受了新辅助 PDT, 在 1 年随访期内无复发^[29]。同样地, 对于特殊部位(如唇部)的 SCC, 新辅助 PDT 可显著减小肿瘤体积, 减轻后遗症^[30-31]。在另一项前瞻性研究中, 33 例 EMPD 患者接受新辅助 PDT 后, 其病变体积平均缩小 58%, 手术创面面积、术后瘢痕均比对照组少^[32]。总之, 新辅助 PDT 对于手术非首选的非黑色素瘤皮肤肿瘤极具价值, 但仍有待大型随机对照试验进一步证实其作为新辅助治疗手段的有效性与安全性。

3 PDT 在感染性皮肤病领域中的应用

感染性皮肤病是由病原体侵入皮肤导致的疾病。皮肤作为人体抵抗外界刺激的第一道防线, 其屏障作用受到破坏, 抵抗病原体入侵的能力下降, 则易发生皮肤感染。在免疫功能正常的患者中, 部分轻微的感染性皮肤病可呈自限性, 而严重的皮肤感染或免疫水平低下的患者发生感染性皮肤病则可能导致死亡。因此, 采取行之有效的治疗方案是提高感染性皮肤病治疗效果的关键。

甲真菌病是最常见的皮肤真菌感染, 约占所有皮肤感染的 1/3, 且患病率有上升趋势, 2%~18% 的人口受到其影响^[33-35]。由于外用药物一般无法穿透指甲, 因此往往需要全身用药, 如使用灰黄霉素、伊曲康唑等药物治疗, 但这可能会出现严重的药物副作用^[36]。PDT 已成为治疗甲真菌病的选择之一, 单线态氧对真菌具有高度的细胞毒性, 并可导致线粒体损伤, 进而引发真菌细胞的程序性死亡^[37]。此外, PDT 具有靶向性与非侵入性, 并且目前尚无 PDT 导致真菌耐药的研究报告^[38]。有研究表明, 基于亚甲蓝的 PDT 对甲真菌病安全有效, 但最佳治疗参数仍需要进一步探索^[39]。

疣是由人乳头瘤病毒(human papilloma virus, HPV)感染皮肤引起的常见皮肤疾病, 传统治疗包括角质剥脱、冷冻、激光、病灶内注射药物等。由于光敏剂可在快速分裂的 HPV 感染细胞中积累, 因此 PDT 可应用于寻常疣的治疗。一项 Meta 分析结果显示, 对于寻常疣, PDT 的清除率高于其他激光治疗(强脉冲激光、脉冲染料激光治疗等), 与病灶内注射维生素 D 相似; 对于扁平疣, PDT 的治愈率高于冷冻治疗^[40]。此外, 使用纳米技术等改进光敏剂递送策略有助于进一步提高 PDT 对疣的疗效^[41]。

尖锐湿疣是一种性传播疾病, 其常见于肛门生殖器区域, 与感染某些类型的 HPV 相关。PDT 对尖锐湿疣的清除率与二氧化碳激光相似, 且可降低复发率^[42]。此外, PDT 与冷冻疗法或二氧化碳激光等局部疗法相结合可进一步提高尖锐湿疣清除率, 降低复发率^[43-44]。有学者在比较多种尖锐湿疣治疗方式后指出, 尖锐湿疣的最佳治疗方案取决于病变大小: 若病变大小 < 0.5 cm, 首选 ALA-PDT; 若病变大小在 0.5~2 cm 之间, 首选治疗方案为冷冻治疗后立即行 ALA-PDT; 若病变大小 > 2 cm, 首选治疗方案为冷冻治疗后病变消失再行 ALA-PDT 或二氧化碳激光治疗^[45]。

4 光动力治疗在其他皮肤疾病领域中的应用

寻常痤疮是一种常见的毛囊皮脂腺炎症性疾病, 可表现为皮脂渗出、闭合性或开放性粉刺、脓疱、丘疹、瘢痕等^[46]。由于皮脂腺单位参与了脂质与激素代谢, 因此疏水性光敏剂亦可被皮脂腺单位摄取, 且可优先在毛囊皮脂腺部位积累, 从而提高 PDT 的选择性抗菌、抗炎作用^[47-48]。一项 Meta 分析结果显示, ALA-PDT、MAL-PDT 及亚甲蓝脂质体凝胶 PDT 均可有效减轻寻常痤疮部位的炎症^[49]。PDT 治疗寻常痤疮的不良反应包括糜烂、红斑、疼痛等, 日光 PDT 及分步 PDT (40 mW/cm² 治疗 5 min、80 mW/cm² 治疗 12.5 min、40 mW/cm² 治疗 5 min) 可有效减少不良反应的发生^[50-51]。此外, 在服用抗生素及类维 A 酸基础上应用 PDT 亦有助于减轻皮肤炎症^[52]。

光老化是由长期日光照射引起的皮肤损伤, 可表现为皮肤松弛、色素沉着、干燥、粉刺等, 可随年龄增加逐渐积累^[53-54]。防晒是预防皮肤光老化的重点, 治疗方面可选用化学换肤术、微针治疗、激光美容等。PDT 是治疗光老化的新兴策略(推荐强度 A 级)^[55]。一项安慰剂随机对照临床试验结果显示, 光老化患者接受两次 MAL-PDT 治疗后, 其皮肤细纹、色素沉着、粗糙、红斑等表现可得到改善^[56]。一项前瞻性对照研究结果显示, 使用强脉冲光联合 ALA-PDT 治疗

的光老化患者的整体评分、细纹及粗纹的改善程度优于单独使用强脉冲光治疗(整体评分分别为50.0%、12.5%,细纹的改善程度分别为70.8%、33.3%,粗纹的改善程度分别为50.0%、12.5%),而副作用为红斑、水肿等光毒性反应^[57]。

皮肤伤口愈合是一个复杂的动态过程^[58-59],近期研究表明,低剂量PDT可促进伤口愈合^[60]。一项临床研究结果显示,7例耐甲氧西林金黄色葡萄球菌和铜绿假单胞菌的皮肤溃疡患者使用0.5% ALA-PDT后,有6例患者的溃疡面积明显减小,且ALA-PDT的安全性令人满意^[61]。另一项临床研究结果显示,3例慢性难治性感染性小腿溃疡患者使用2% ALA-PDT治疗后溃疡完全愈合,且一次治疗后均未在治疗区域分离出细菌^[62]。另外,亚甲蓝光PDT亦对皮肤伤口具有类似的效果^[63]。PDT促进皮肤伤口愈合的可能机制包括促进成纤维细胞迁移^[64]、促进肉芽组织重塑及血管生成等^[65]。

糖尿病足溃疡是糖尿病常见的并发症之一,由于伤口愈合延迟、易于感染、肿胀渗出等,部分患者被迫截肢。PDT因具有抗炎、抗菌、免疫调节等作用,已被应用于糖尿病足溃疡患者的治疗^[66-67]。多项临床研究表明,PDT对糖尿病足溃疡的疗效优于单用胶原酶/氯霉素治疗^[68]、安慰剂治疗^[69]、抗生素治疗联合常规外科治疗^[70]等措施。一项Meta分析结果显示,PDT在组织修复、控制微生物感染等方面具有良好效果,大幅降低了糖尿病足溃疡患者的截肢率^[67]。

病理性瘢痕包括瘢痕疙瘩与增生性瘢痕,由于伤口愈合异常,其可引起疼痛、瘙痒等症状。一例纳入10例瘢痕疙瘩患者的临床研究结果显示,手术联合放疗后使用ALA-PDT可减小瘢痕体积,并减轻瘙痒、疼痛等不适^[71]。另外,微针治疗辅助ALA-PDT或二氧化碳激光联合ALA-PDT对增生性瘢痕的疗效与病灶内注射糖皮质激素相当,而6个月随访期内复发率更低^[72]。一项自身对照临床研究结果显示,对于下颌骨病理性瘢痕,可选用环钻联合ALA-PDT作为治疗方案^[73]。PDT对病理性瘢痕的治疗机制尚未明确,目前认为可能与抑制成纤维细胞活动、促进胶原重塑有关^[74-75]。

口腔黏膜白斑病(oral leukoplakia, OLK)是一种发生于口腔黏膜、以白色斑块为表现的病变,非均质性OLK的恶变风险较高^[76]。当病变广泛或部位特殊时,手术难度大并可能存在毁容风险^[77-78]。ALA-PDT是治疗OLK的潜在替代疗法,有效率达50%~100%,完全缓解率为16.49%~88.89%^[79-80]。

硬化性苔藓(Lichen sclerosus, LS)是一种好发于生殖器区域的慢性炎症性疾病,往往导致皮肤瘢痕及萎缩。传统疗法包括外用糖皮质激素、钙调神经磷酸酶抑制剂等,但效果欠佳^[81]。ALA-PDT是治疗LS的潜在

有效手段,有效率达52.0%~87.5%^[82-83]。一项随机对照试验表明,ALA-PDT对LS的完全缓解率和持续控制效果优于丙酸氯倍他索^[84]。对于其他治疗失败的难治性LS,ALA-PDT可明显改善患者的临床症状^[85]。

5 小结与展望

PDT具有靶向性高的优势,其在皮肤疾病领域应用的有效性与安全性已得到初步证实。随着对PDT认识的深入,PDT的适应证正在迅速扩大。越来越多的临床证据表明,PDT在皮肤肿瘤及癌前病变、各类微生物皮肤感染及其他皮肤疾病中均取得了优越的治疗效果。此外,PDT联合其他疗法或作为辅助治疗也取得了卓有成效的进展。

现阶段PDT还存在一些不足:首先,部分适应证仍处于临床试验阶段,未形成指南或专家共识,治疗参数的差异可能导致疗效不一致。其次,PDT可能导致治疗时及治疗后疼痛,仍需要进一步优化治疗流程,改进麻醉策略、护理策略等。此外,现有光敏剂成本较高,PDT价格较昂贵。

提升安全性与稳定性、降低成本可能是未来PDT的发展方向之一^[86]。新型光敏剂的研发有助于进一步提高光敏剂在靶组织的特异性聚集,以及获取更高的单线态氧产率。纳米技术、生物学医学工程技术、人工智能等新技术已投入于新型光敏剂的探索中^[87]。研发新型的光照电子器件,开发近红外II区的PDT策略,可实现更深层次的皮肤治疗。此外,开发更精确的治疗监测与反馈系统,实时追踪PDT的效果并调整参数,有助于实现个体化的精准治疗,减轻烧灼感、疼痛等副作用。最后,仍需要加强基础科研转化并开展大规模III期、IV期临床试验,获取更多临床证据,进一步证实PDT对皮肤疾病的有效性与安全性,并优化治疗方案与流程,在提高疗效的同时改善患者的就医体验感。

参 考 文 献

- [1] 中华医学会皮肤性病学分会光动力治疗研究中心,中国康复医学会皮肤病康复专业委员会,中国医学装备协会皮肤病与皮肤美容分会光医学治疗装备学组. 氨基酮戊酸光动力疗法皮肤科临床应用指南(2021版)[J]. 中华皮肤科杂志, 2021, 54(1): 1-9.
- [2] Morton CA, Szeimies RM, Basset-Seguin N, et al. European Dermatology Forum guidelines on topical photodynamic therapy 2019 part 1: treatment delivery and established indications-actinic keratoses, Bowen's disease and basal cell carcinomas[J]. J Eur Acad Dermatol Venereol, 2019, 33(12): 2225-2238.

- [3] Feng GX, Zhang GQ, Ding D. Design of superior phototheranostic agents guided by Jablonski diagrams [J]. *Chem Soc Rev*, 2020, 49(22):8179–8234.
- [4] Gai S, Yang G, Yang A, et al. Recent advances in functional nanomaterials for light-triggered cancer therapy [J]. *Nano Today*, 2018, 19:146–187.
- [5] Dolmans DE, Fukumura DJR. Photodynamic therapy for cancer [J]. *Nat Rev Cancer*, 2003, 3(5):380–387.
- [6] Heerfordt IM, Wulf HC. Daylight photodynamic therapy of actinic keratosis without curettage is as effective as with curettage: a randomized clinical trial [J]. *J Eur Acad Dermatol Venereol*, 2019, 33(11):2058–2061.
- [7] Li X, Wang H, Li Z, et al. Oxygen tank for synergistic hypoxia relief to enhance mitochondria-targeted photodynamic therapy [J]. *Biomater Res*, 2022, 26(1):47.
- [8] Li Z, Wang C, Deng H, et al. Robust photodynamic therapy using 5-ALA-Incorporated nanocomplexes cures metastatic melanoma through priming of CD4⁺CD8⁺ double positive T cells [J]. *Adv Sci*, 2019, 6(5):1802057.
- [9] Balakirski G, Lehmann P, Szeimies RM, et al. Photodynamic therapy in dermatology: established and new indications [J]. *J Dtsch Dermatol Ges*, 2024, 22(12):1651–1662.
- [10] Ozog DM, Rkein AM, Fabi SG, et al. Photodynamic therapy: a clinical consensus guide [J]. *Dermatol Surg*, 2016, 42(7):804–827.
- [11] Szeimies RM, Ibbotson S, Murrell DF, et al. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8–20 mm), with a 12-month follow-up [J]. *J Eur Acad Dermatol Venereol*, 2008, 22(11):1302–1311.
- [12] Rhodes LE, de Rie MA, Leifsdottir R, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy *vs* surgery for nodular basal cell carcinoma [J]. *Arch Dermatol*, 2007, 143(9):1131–1136.
- [13] Roozeboom MH, Aardoom MA, Nelemans PJ, et al. Fractionated 5-aminolevulinic acid photodynamic therapy after partial debulking versus surgical excision for nodular basal cell carcinoma: a randomized controlled trial with at least 5-year follow-up [J]. *J Am Acad Dermatol*, 2013, 69(2):280–287.
- [14] Torres T, Fernandes I, Costa V, et al. Photodynamic therapy as adjunctive therapy for morpheaform basal cell carcinoma [J]. *Acta Dermatoven*, 2011, 20(1):23–25.
- [15] Liu X, Wang J, Yu JP, et al. Experience analysis of a combined photodynamic/electrodesiccation therapy in the treatment of 11 cases of large patches of Bowen's disease [J]. *Photodiagnosis Photodyn Ther*, 2023, 43:103710.
- [16] Kibbi N, Zhang YM, Leffell DJ, et al. Photodynamic therapy for cutaneous squamous cell carcinoma in situ: impact of anatomic location, tumor diameter, and incubation time on effectiveness [J]. *J Am Acad Dermatol*, 2020, 82(5):1124–1130.
- [17] Storer M, Zhu Z, Sokil M, et al. Community-based practice variations in topical treatment of actinic keratoses [J]. *JAMA Dermatol*, 2017, 153(5):468–470.
- [18] Hu CJ, Luo XY, Jiang CF, et al. Efficacy and safety of photodynamic therapy for the treatment of actinic keratoses: a meta-analysis update of randomized controlled trials [J]. *Dermatol Surg*, 2023, 49(6):544–551.
- [19] Dirschka T, Radny P, Dominicus R, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolevulinate cream and placebo [J]. *Br J Dermatol*, 2012, 166(1):137–146.
- [20] Talpur R, Singh L, Daulat S, et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sézary syndrome from 1982 to 2009 [J]. *Clin Cancer Res*, 2012, 18(18):5051–5060.
- [21] Dummer R, Vermeer MH, Scarisbrick JJ, et al. Cutaneous T cell lymphoma [J]. *Nat Rev Dis Primers*, 2021, 7(1):61.
- [22] Mehta-Shah N, Horwitz SM, Ansell S, et al. Primary cutaneous lymphomas, version 2.2020. Featured updates to the NCCN guidelines [J]. *J Natl Compr Canc Netw*, 2020, 18(5):522–536.
- [23] Kim EJ, Mangold AR, DeSimone JA, et al. Efficacy and safety of topical hypericin photodynamic therapy for early-stage cutaneous T-cell lymphoma (mycosis fungoides): the FLASH phase 3 randomized clinical trial [J]. *JAMA Dermatol*, 2022, 158(9):1031–1039.
- [24] Kibbi N, Owen JL, Worley B, et al. Evidence-based clinical practice guidelines for extramammary paget disease [J]. *JAMA Oncol*, 2022, 8(4):618–628.
- [25] Ren F, Zhao ST, Yang CX, et al. Applications of photodynamic therapy in extramammary Paget's disease [J]. *Am J Cancer Res*, 2023, 13(10):4492–4507.
- [26] Shim PJ, Zeitouni NC. Photodynamic therapy for extramammary Paget's disease: a systematic review of the literature [J]. *Photodiagnosis Photodyn Ther*, 2020, 31:101911.
- [27] Lin JD, Li MH, Wu TH, et al. Combined methyl aminolevulinate-based photodynamic therapy and imiquimod in a patient with perianal extramammary Paget's disease [J]. *Photodiagnosis Photodyn Ther*, 2021, 35:102407.
- [28] Li X, Zhao C, Kou H, et al. PDD-guided tumor excision combined with photodynamic therapy in patients with extramammary Paget's disease [J]. *Photodiagnosis Photodyn Ther*, 2022, 38:102841.
- [29] Yan J, Wang B, Zhang GL, et al. Neoadjuvant photodynamic therapy: an updated therapeutic approach for non-melanoma skin cancers [J]. *Curr Treat Options Oncol*, 2024, 25(6):813–826.
- [30] Yan J, Wang P, Li L, et al. Surgery sequential with 5-aminolevulinic acid photodynamic therapy for lip squamous cell carcinoma: two cases reports [J]. *Photodiagnosis Photodyn Ther*, 2020, 32:102043.
- [31] Wang P, Zhang G, Zhang L, et al. 5-Aminolevulinic acid photodynamic therapy for early-stage lip squamous cell carcinoma [J]. *Photodiagnosis Photodyn Ther*, 2021, 35:102321.
- [32] Li C, Guo L, Wang P, et al. ALA-PDT combined with holmium laser therapy of postoperative recurrent extramammary Paget's disease [J]. *Photodiagnosis Photodyn Ther*, 2019, 27:92–94.

- [33] Gupta AK, Stec N, Summerbell RC, et al. Onychomycosis: a review[J]. *J Eur Acad Dermatol Venereol*, 2020, 34(9): 1972–1990.
- [34] Carney C, Tosti A, Daniel R, et al. A new classification system for grading the severity of onychomycosis: onychomycosis severity index[J]. *Arch Dermatol*, 2011, 147(11): 1277–1282.
- [35] Gupta AK, Shear NH. Onychomycosis. Going for cure [J]. *Can Fam Physician*, 1997, 43: 299–305.
- [36] Daggett C, Brodell RT, Daniel CR, et al. Onychomycosis in athletes[J]. *Am J Clin Dermatol*, 2019, 20(5): 691–698.
- [37] Ortiz AE, Avram MM, Wanner MA. A review of lasers and light for the treatment of onychomycosis [J]. *Lasers Surg Med*, 2014, 46(2): 117–124.
- [38] Silva APD, Kurachi C, Bagnato VS, et al. Fast elimination of onychomycosis by hematoporphyrin derivative - photodynamic therapy [J]. *Photodiagnosis Photodyn Ther*, 2013, 10(3): 328–330.
- [39] Alberdi E, Gómez C. Efficiency of methylene blue-mediated photodynamic therapy vs intense pulsed light in the treatment of onychomycosis in the toenails [J]. *Photodermatol Photoimmunol Photomed*, 2019, 35(2): 69–77.
- [40] Shen S, Feng J, Song X, et al. Efficacy of photodynamic therapy for warts induced by human papilloma virus infection: a systematic review and meta-analysis [J]. *Photodiagnosis Photodyn Ther*, 2022, 39: 102913.
- [41] Fadel M, Kassab K, Samy N, et al. Nanovesicular photodynamic clinical treatment of resistant plantar warts [J]. *Curr Drug Deliv*, 2020, 17(5): 396–405.
- [42] Liang J, Lu XN, Tang H, et al. Evaluation of photodynamic therapy using topical aminolevulinic acid hydrochloride in the treatment of condylomata acuminata; a comparative, randomized clinical trial [J]. *Photodermatol Photoimmunol Photomed*, 2009, 25(6): 293–297.
- [43] Mi X, Chai W, Zheng H, et al. A randomized clinical comparative study of cryotherapy plus photodynamic therapy vs. cryotherapy in the treatment of multiple condylomata acuminata [J]. *Photodermatol Photoimmunol Photomed*, 2011, 27(4): 176–180.
- [44] Zhu X, Chen H, Cai L, et al. Decrease recurrence rate of condylomata acuminata by photodynamic therapy combined with CO₂ laser in Mainland China: a meta-analysis [J]. *Dermatology*, 2012, 225(4): 364–370.
- [45] Shi H, Zhang X, Ma C, et al. Clinical analysis of five methods used to treat condylomata acuminata [J]. *Dermatology*, 2013, 227(4): 338–345.
- [46] Zhao JM, Wang Y, Jiang L, et al. The application of skin care product in acne treatment [J]. *Dermatol Ther (Heidelb)*, 2020, 33(6): e14287.
- [47] Divaris DX, Kennedy JC, Pottier RH. Phototoxic damage to sebaceous glands and hair follicles of mice after systemic administration of 5-aminolevulinic acid correlates with localized protoporphyrin IX fluorescence [J]. *Am J Pathol*, 1990, 136(4): 891–897.
- [48] Luo OD, Bose R, Bawazir MA, et al. A review of the dermatologic clinical applications of topical photodynamic therapy [J]. *J Cutan Med Surg*, 2024, 28(1): NP1.
- [49] Tang XQ, Li CC, Ge SQ, et al. Efficacy of photodynamic therapy for the treatment of inflammatory acne vulgaris: a systematic review and meta-analysis [J]. *J Cosmet Dermatol*, 2020, 19(1): 10–21.
- [50] Slutsky-Bank E, Artzi O, Sprecher E, et al. A split-face clinical trial of conventional red-light photodynamic therapy versus daylight photodynamic therapy for acne vulgaris [J]. *J Cosmet Dermatol*, 2021, 20(12): 3924–3930.
- [51] Wu HE, Liu YB, Cui L, et al. Three-step irradiance schedule versus two-step irradiance schedule for pain control during topical 5-aminolevulinic acid-photodynamic therapy of facial acne in Chinese patients: a prospective randomized comparative study [J]. *Lasers Surg Med*, 2022, 54(2): 224–229.
- [52] Nicklas C, Rubio R, Cárdenas C, et al. Comparison of efficacy of aminolevulinic acid photodynamic therapy vs. adapalene gel plus oral doxycycline for treatment of moderate acne vulgaris—a simple, blind, randomized, and controlled trial [J]. *Photodermatol Photoimmunol Photomed*, 2019, 35(1): 3–10.
- [53] Kammeyer A, Luiten RM. Oxidation events and skin aging [J]. *Ageing Res Rev*, 2015, 21: 16–29.
- [54] Zou ZR, Long X, Zhao Q, et al. A Single-cell transcriptomic atlas of human skin aging [J]. *Dev Cell*, 2021, 56(3): 383–397.e8.
- [55] Shi L, Wang H, Chen K, et al. Chinese guidelines on the clinical application of 5-aminolevulinic acid-based photodynamic therapy in dermatology (2021 edition) [J]. *Photodiagnosis Photodyn Ther*, 2021, 35: 102340.
- [56] Sanclemente G, Medina L, Villa JF, et al. A prospective split-face double-blind randomized placebo-controlled trial to assess the efficacy of methyl aminolevulinate + red-light in patients with facial photodamage [J]. *J Eur Acad Dermatol Venereol*, 2011, 25(1): 49–58.
- [57] Xi Z, Shuxian Y, Zhong L, et al. Topical 5-aminolevulinic acid with intense pulsed light versus intense pulsed light for photodamage in Chinese patients [J]. *Dermatol Surg*, 2011, 37(1): 31–40.
- [58] Grandi V, Corsi A, Pimpinelli N, et al. Cellular mechanisms in acute and chronic wounds after PDT therapy: an update [J]. *Biomedicines*, 2022, 10(7): 1–10.
- [59] Yang T, Tan Y, Zhang WT, et al. Effects of ALA-PDT on the healing of mouse skin wounds infected with *Pseudomonas aeruginosa* and its related mechanisms [J]. *Front Cell Dev Biol*, 2020, 8: 585132.
- [60] Zhang YW, Liu W, Wang Q. Positive effects of low-dose photodynamic therapy with aminolevulinic acid or its methyl ester in skin rejuvenation and wound healing: an update [J]. *J Biophotonics*, 2023, 16(4): e202200293.
- [61] Shiratori M, Ozawa T, Ito N, et al. Open study of photodynamic therapy for skin ulcers infected with MRSA and *Pseudomonas aeruginosa* [J]. *Photodiagnosis Photodyn Ther*, 2021, 36: 102484.

- [62] Lin MH, Lee JYY, Pan SC, et al. Enhancing wound healing in recalcitrant leg ulcers with aminolevulinic acid-mediated antimicrobial photodynamic therapy [J]. Photodiagnosis Photodyn Ther, 2021, 33: 102149.
- [63] Cesar GB, Winyk AP, Sluchensci Dos Santos F, et al. Treatment of chronic wounds with methylene blue photodynamic therapy: a case report [J]. Photodiagnosis Photodyn Ther, 2022, 39: 103016.
- [64] Khorsandi K, Fekrazad R, Hamblin MR. Low-dose photodynamic therapy effect on closure of scratch wounds of normal and diabetic fibroblast cells: an *in vitro* study [J]. J Biophotonics, 2021, 14(7): e202100005.
- [65] Yang Z, Hu X, Zhou L, et al. Photodynamic therapy accelerates skin wound healing through promoting re-epithelialization [J]. Burns Trauma, 2021, 9: tkab008.
- [66] Martinelli N, Curci V, Quarantiello A, et al. The benefits of antimicrobial photodynamic therapy with RLP068 in the management of diabetic foot ulcers [J]. Drugs Context, 2019, 8: 212610.
- [67] Brandão MGSA, Ximenes MAM, Sousa DFD, et al. Photodynamic therapy for infected foot ulcers in people with diabetes mellitus: a systematic review [J]. Sao Paulo Med J, 2023, 141(6): e2022476.
- [68] Carrinho PM, Andreani DIK, Morete VDA, et al. A study on the macroscopic morphometry of the lesion area on diabetic ulcers in humans treated with photodynamic therapy using two methods of measurement [J]. Photomed Laser Surg, 2018, 36(1): 44-50.
- [69] Morley S, Griffiths J, Philips G, et al. Phase II a randomized, placebo-controlled study of antimicrobial photodynamic therapy in bacterially colonized, chronic leg ulcers and diabetic foot ulcers: a new approach to antimicrobial therapy [J]. Br J Dermatol, 2013, 168(3): 617-624.
- [70] Tardivo JP, Adami F, Correa JA, et al. A clinical trial testing the efficacy of PDT in preventing amputation in diabetic patients [J]. Photodiagnosis Photodyn Ther, 2014, 11(3): 342-350.
- [71] Bu WB, Fang F, Zhang ML, et al. Combination of 5-ALA photodynamic therapy, surgery and superficial X-ray for the treatment of keloid [J]. Photodermatol Photoimmunol Photomed, 2020, 36(1): 65-67.
- [72] Yan DM, Zhao HY, Li CX, et al. A clinical study of carbon dioxide lattice laser-assisted or microneedle-assisted 5-aminolevulinic acid-based photodynamic therapy for the treatment of hypertrophic acne scars [J]. Photodermatol Photoimmunol Photomed, 2022, 38(1): 53-59.
- [73] Luo XY, Wu XG, Xu AE, et al. The combination of the mini-punch technique and photodynamic therapy for the treatment of mandibular keloids and hypertrophic scars [J]. Dermatol Surg, 2022, 48(12): 1294-1298.
- [74] Zhang J, Liu L, Li X, et al. 5-ALA-PDT induced ferroptosis in keloid fibroblasts *via* ROS, accompanied by downregulation of xCT, GPX4 [J]. Photodiagnosis Photodyn Ther, 2023, 42: 103612.
- [75] Wang X, Cao P, Liu J, et al. 5-Aminolaevulinic acid-based photodynamic therapy restrains pathological hyperplasia of fibroblasts [J]. Med Sci Monit, 2017, 23: 46-56.
- [76] 中华口腔医学会口腔黏膜病专业委员会. 口腔白斑病的定义与分级标准(试行) [J]. 中华口腔医学杂志, 2011, 46(10): 579-580.
- [77] Kumar A, Cascarini L, McCaul JA, et al. How should we manage oral leukoplakia? [J]. Br J Oral Maxillofac Surg, 2013, 51(5): 377-383.
- [78] Awadallah M, Idle M, Patel K, et al. Management update of potentially premalignant oral epithelial lesions [J]. Oral Surg Oral Med Oral Pathol Oral Radiol, 2018, 125(6): 628-636.
- [79] Yao Y, Shen X, Shi L, et al. The combination of photodynamic therapy and fractional CO₂ laser for oral leukoplakia: case series [J]. Photodiagnosis Photodyn Ther, 2020, 29: 101597.
- [80] Chen QM, Dan HX, Tang F, et al. Photodynamic therapy guidelines for the management of oral leucoplakia [J]. Int J Oral Sci, 2019, 11(2): 14.
- [81] Liu J, Hao J, Wang Y, et al. Clinical and dermoscopic assessment of vulvar lichen sclerosis after 5-aminolevulinic acid photodynamic therapy: a prospective study [J]. Photodiagnosis Photodyn Ther, 2021, 33: 102109.
- [82] Maździarz A, Osuch B, Kowalska M, et al. Photodynamic therapy in the treatment of vulvar *Lichen sclerosis* [J]. Photodiagnosis Photodyn Ther, 2017, 19: 135-139.
- [83] Prodromidou A, Chatziioannou E, Daskalakis G, et al. Photodynamic therapy for vulvar *Lichen sclerosis* - a systematic review [J]. J Low Genit Tract Dis, 2018, 22(1): 58-65.
- [84] Shi L, Miao F, Zhang LL, et al. Comparison of 5-aminolevulinic acid photodynamic therapy and clobetasol propionate in treatment of vulvar *Lichen sclerosis* [J]. Acta Derm Venereol, 2016, 96(5): 684-688.
- [85] Zheng X, Liu X, Zhang J, et al. 5-aminolevulinic acid photodynamic therapy is a safe and effective treatment for female patients with intractable vulvar *Lichen sclerosis* [J]. Photodiagnosis Photodyn Ther, 2024, 49: 104330.
- [86] Li Z, Li X, Lu Y, et al. Novel photo-STING agonists delivered by erythrocyte efferocytosis-mimicking pattern to repolarize tumor-associated macrophages for boosting anticancer immunotherapy [J]. Adv Mater, 2024, 36(47): 2410937.
- [87] Rao L, Yuan Y, Shen X, et al. Designing nanotheranostics with machine learning [J]. Nat Nanotechnol, 2024, 19(12): 1769-1781.

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