Energy-Based Devices for Actinic Keratosis Field Therapy

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PRACTICE **POINTS**

- Ablative fractional laser therapy in combination with photodynamic therapy has demonstrated increased efficacy in treating field actinic keratoses (AKs) for up to 12 months of follow-up over either modality alone.
- Ablative and nonablative lasers as monotherapy in treating field AKs require further studies with larger sample sizes to determine efficacy and safety.

Cutaneous field cancerization arises due to UV-induced carcinogenesis of a "field" of subclinically transformed skin and actinic keratoses (AKs) with a tendency to progress and recur. Commonly used treatment methods for multiple AKs include imiquimod, fluorouracil, ingenol mebutate, and photodynamic therapy; however, new options in field-directed therapy with superior efficacy, cosmesis, and convenience may appeal to patients. Ablative and nonablative lasers may fulfill these advantages and have been investigated as monotherapies and combination therapies for field cancerization. In this article, a review of the literature on various laser modalities with a focus on efficacy is provided.

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In cutaneous field cancerization, focal treatments such as cryotherapy are impractical, thus necessitating the use of field-directed therapies over the lesion and the surrounding skin field. Although evidence-based guidelines do not exist, field-directed therapy has been proposed in cases of 3 or more actinic keratoses (AKs) in a 25-cm^2 area or larger.[1] It can be further speculated that patients who are vulnerable to aggressive phenotypes of cutaneous malignancies, such as those with a genodermatosis or who are immunocompromised, necessitate a higher index of suspicion for field effect with even 1 or 2 AKs.

Current field-directed therapies include topical agents (imiquimod, fluorouracil, ingenol mebutate, and diclofenac), photodynamic therapy (PDT), and resurfacing procedures (lasers, chemical peels, dermabrasion). Although topical agents and PDT currently are gold standards in field treatment, the use of energy-based devices (ie, ablative and nonablative lasers) are attractive options as monotherapy or as part of a combination therapy. These devices are attractive options for field-directed therapy because they offer defined, customizable control of settings, allowing for optimal cosmesis and precision of therapy.

Principally, lasers function by damaging skin tissue to induce resurfacing, neocollagenesis, and vascular restructuring. Fractional versions of ablative and nonablative systems are available to target a fraction of the treatment area in evenly spaced microthermal zones and to minimize overall thermal damage.[2]

Given recent advances in laser systems and numerous investigations reported in the literature, a review of ablative and nonablative lasers that have been studied as treatment options for cutaneous field cancerization is provided, with a focus on treatment efficacy.

Ablative Lasers

Ablative lasers operate at higher wavelengths than nonablative lasers to destroy epidermal and dermal tissue. The 10,600-nm carbon dioxide (CO_2) and 2940-nm Er:YAG lasers have been heavily investigated for field therapy for multiple AKs, both as monotherapies (Table 1) and in combination with PDT (Table 2).

Monotherapy—One randomized trial with 5-year follow-up compared the efficacy of full-face pulsed CO_2 laser therapy, full-face trichloroacetic acid (TCA) peel 30%,

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TABLE 1. Pulsed 10,600-nm Carbon Dioxide Laser as Monotherapy for AK Field Treatment

Reference (Year)	Treatment Arms	No. of Participants	Laser Settings	Results
Hantash et al[3] (2006)	CO_2 laser vs TCA peel 30% vs fluorouracil cream 5%	34 (24 randomized to treatment groups, 7 controls); 3 excluded for violating treatment protocol	Energy: not reported; Power: 5–6 W; No. of passes: 2	CO_2 laser group: 92% reduction in AK count from baseline (*P*=.03); TCA group: 89% (*P*=.004); fluorouracil group: 83% (*P*=.008); no significant differences in efficacy among treatment groups
Gan et al[4] (2016)	Split-face study: CO_2 laser vs no treatment	12 (3 lost to follow-up)	Energy: 70 MJ/pulse; Power: 9 W; Density: 4; No. of passes: 1	Baseline reduction in AK count: 47% (CO_2 laser side) vs 71% (untreated side) at 1-mo follow-up; results were not sustained at 3-mo follow-up
Scola et al[5] (2012)	Split-body study: CO_2 laser vs ALA-PDT	21 (1 did not complete study)	Energy: 150 MJ; Power: 1.5 W; Frequency: 10 Hz; Density: 1	ALA-PDT group had significantly greater reduction in AK count versus CO_2 laser group (*P*=.0362)

Abbreviations: AK, actinic keratosis; CO_2, carbon dioxide; TCA, tricholoracetic acid; ALA, aminolevulinic acid; PDT, photodynamic therapy.

and fluorouracil cream 5% (twice daily for 3 weeks) on AKs on the face and head.[3] Thirty-one participants were randomized to the 3 treatment arms and a negative control arm. The mean AK counts at baseline for the CO_2, TCA, and fluorouracil treatment groups were 78.0, 83.7, and 61.8, respectively. At 3-month follow-up, all treatment groups had significant reductions in the mean AK count from baseline (CO_2 group, 92% [*P*=.03]; TCA group, 89% [*P*=.004]; fluorouracil group, 83% [*P*=.008]). No significant differences in efficacy among the treatment groups were noted. All 3 treatment groups had a demonstrably lower incidence of nonmelanoma skin cancer over 5-year follow-up compared to the control group (*P*<.001).[3]

In contrast to these promising results, the pulsed CO_2 laser showed only short-term efficacy in a split-face study of 12 participants with at least 5 facial or scalp AKs on each of 2 symmetric facial sides who were randomized to 1 treatment side.[4] At 1-month follow-up, the treatment side exhibited significantly fewer AKs compared to the control side (47% vs 71% at baseline; *P*=.01), but the improvement was not sustained at 3-month follow-up (49% vs 57%; *P*=.47).[4]

In another study, the CO_2 laser was found to be inferior to 5-aminolevulinic acid PDT.[5] Twenty-one participants who had at least 4 AKs in each symmetric half of a body region (head, hands, forearms) were randomized to PDT on 1 side and CO_2 laser therapy on the other. Median baseline AK counts for the PDT and CO_2 laser groups were 6 and 8, respectively. Both treatment groups exhibited significant median AK reduction from baseline 4 weeks posttreatment (PDT group, 82.1% [*P*<.05], CO_2 laser group, 100% [*P*<.05]); however. at 3 months posttreatment the PDT group had significantly higher absolute (*P*=.0155) and relative (*P*=.0362) reductions in AK count compared to the CO_2 laser group. One participant received a topical antibiotic for superficial infection on the PDT treatment side.[5]

Many questions remain regarding the practical application of laser ablation monotherapy for multiple AKs. More studies are needed to determine the practicality and long-term clinical efficacy of these devices.

PDT Combination Therapy—Laser ablation may be combined with PDT to increase efficacy and prolong remission rates. In fact, laser ablation may be thought of as a physical drug-delivery system to boost uptake of topical agents—in this case, aminolevulinic acid and methyl aminolevulinate (MAL)—given that it disrupts the skin barrier.

In a comparative study of ablative fractional laser (AFXL)–assisted PDT and AFXL alone in 10 organ transplant recipients on immunosuppression with at least 5 AKs on each dorsal hand, participants were randomized to AFXL-PDT on one treatment side and PDT on the other side.[6] Participants received AFXL in an initial lesion-directed pass and then a second field-directed pass of a fractional CO_2 laser. After AFXL exposure, methyl aminolevulinate was applied to the AFXL-PDT treatment side, with 3-hour occlusion. A total of 680 AKs were treated (335 in the AFXL-PDT group, 345 in the PDT group); results were stratified by the clinical grade of the lesion (1, slightly palpable; 2, moderately thick; 3, very thick or obvious). At 4-month follow-up, the AFXL-PDT group had a significantly higher median complete response rate of 73% compared to 31% in the AFXL group (*P*=.002). Interestingly, AFXL-PDT was also significantly more efficacious compared to AFXL for grades 1 (80% vs 37%; *P*=.02) and 2 (53% vs 7%, *P*=.009) AKs but not grade 3 AKs (4% vs 0%, *P*=.17).[6]

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TABLE 2. Combination Therapy With Ablative Lasers and Photodynamic Therapy for AK Field Treatment

Reference (Year)	Combination Therapy	No. of Participants	Laser Settings	PDT Protocol	Results	Adverse Events
Helsing et al[6] (2013)	Split-body: AFXL (CO_2 laser) and MAL-PDT vs AFXL alone	10 (OTRs)	Wavelength: 10,600 nm; Power: 30 W; Energy: 140 MJ/pulse or 160 MJ/pulse (first pass), 40 MJ/pulse or 60 MJ/pulse (2nd pass); Pulse duration: 5.65 ms or 6.25 ms (1st pass), 1.32 or 2.06 ms (2nd pass); Density: 5.2% or 5.3% (1st pass), 4.3% or 5.3% (2nd pass)	Wavelength: 632 nm; Dosage: 37 J/cm^2; Occlusion: 3 hr	AFXL-PDT had higher complete response rates than AFXL alone (73% vs 31%; *P*=.002)	Inflammation (n=3), purpura (n=3), edema (n=3), pain (n=3)
Togsverd-Bo et al[7] (2012)	Split-face: AFXL (CO_2 laser) and MAL-PDT vs MAL-PDT alone	15	Wavelength: 10,600 nm; Energy: 10 MJ/pulse; Density: 5%	Wavelength: 632 nm; Dosage: 37 J/cm^2; Occlusion: 3 hr	AFXL and MAL-PDT had a higher rate of complete response than MAL-PDT alone (90% vs 67%; *P*=.0002)	Pain (n=15); erythema (n=15); crusting (n=15); inflammation (n=15); pigmentary changes (AFXL-PDT, n=6; PDT alone, n=2)
Choi et al[8] (2015)	Split-body: AFXL (Er:YAG laser) and MAL-PDT (3-hr occlusion) vs AFXL (Er:YAG laser) and MAL-PDT (2-hr occlusion) vs MAL-PDT (3-hr occlusion)	93	Wavelength: 2940 nm; Density: 22%	Wavelength: 632 nm; Dosage: 37 J/cm^2	AFXL and MAL-PDT (3-hr occlusion) had the highest rate of complete response compared to AFXL and MAL-PDT (2-hr occlusion) and MAL-PDT alone at 3-mo (91.7% vs 76.8% vs 65.6%; *P*<.001) and 12-mo (84.8% vs 67.5% vs 51.1%; *P*<.001)	Pain during red-light illumination (100%), crusting (78.6%–86.8%), erythema (76.3%–78.1%), hyperpigmentation (74%–75.5%), burning sensation (67.9%–75.9%), pruritus (42%–45.7%), edema (3.8%–7.9%), bullae (4.6%–6.2%); no significant differences in rates across treatment groups
Togsverd-Bo et al[9] (2015)	Split-body: AFXL (Er:YAG laser) and dPDT vs dPDT alone vs cPDT alone vs AFXL alone	16 (OTRs)	Wavelength: 2940 nm; Energy: 2.3 MJ/pulse; Pulse duration: 50 ms; Density: 2.4%	Wavelength: 630 nm; Dosage: 37 J/cm^2; Occlusion: 2.5 hr for dPDT, 3 hr for cPDT; Daylight: 2 hr for AFXL-dPDT and dPDT alone	At 3-mo follow-up, complete response rates were highest for AFXL-dPDT (74%) versus dPDT alone (46% [*P*=.0262]), cPDT alone (50% [*P*=.042]), and AFXL alone (5% [*P*=.004])	PDT-treated areas in all treatment groups: erythema, crusting, inflammation (most severe in AFXL-dPDT); AFXL-dPDT group: pigmentary changes (n=2), dermatitis (n=1)

Abbreviations: AK, actinic keratosis; AFXL, ablative fractional laser; CO_2, carbon dioxide; MAL, methyl aminolevulinate; PDT, photodynamic therapy; OTR, organ transplant recipient; dPDT, daylight photodynamic therapy; cPDT, conventional photodynamic therapy.

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The combination of fractional CO_2 laser and PDT also demonstrated superiority to PDT.[7] In a split-face investigation, 15 participants with bilateral symmetric areas of 2 to 10 AKs on the face or scalp were randomized to receive fractional CO_2 laser and MAL-PDT combination therapy on 1 treatment side and conventional MAL-PDT on the other side.[7] The AFXL-PDT treatment side received laser ablation with immediate subsequent application of MAL to both treatment sides under 3-hour occlusion. At baseline, 103 AKs were treated by AFXL-PDT and 109 AKs were treated with conventional PDT. At 3-month follow-up, the AFXL-PDT treatment group exhibited a significantly higher rate of complete response (90%) compared to the conventional PDT group (67%)(P=.0002).[7]

Like the CO_2 laser, the Er:YAG laser has demonstrated superior results when used in combination with PDT to treat field cancerization compared to either treatment alone. In a comparison study, 93 patients with 2 to 10 AK lesions on the face or scalp were randomized to treatment with AFXL (Er:YAG laser) and MAL-PDT with 3-hour occlusion, AFXL (Er:YAG laser) and MAL-PDT with 2-hour occlusion, and MAL-PDT with 3-hour occlusion.[8] A total of 440 baseline AK lesions on the face or scalp were treated. At 3-month follow-up, the AFXL-PDT (3-hour occlusion) group had the highest rate of complete response (91.7%), compared to 76.8% (P=.001) in the AFXL-PDT (2-hour occlusion) and 65.6% (P=.001) in the PDT groups, regardless of the grade of AK lesion. The AFXL-PDT (2-hour occlusion) treatment was also superior to PDT alone (P=.038). These findings were sustained at 12-month follow-up (84.8% in the AFXL-PDT [3-hour occlusion] group [P<.001, compared to others]; 67.5% in the AFXL-PDT [2-hour occlusion] group [P<.001, compared to 3-hour PDT]; 51.1% in the PDT group). Importantly, the AK lesion recurrence rate was also lowest in the AFL-PDT (3-hour occlusion) group (7.5% vs 12.1% and 22.1% in the AFXL-PDT [2-hour occlusion] and PDT groups, respectively; P=.007).[8]

Combination therapy with AFXL and daylight PDT (dPDT) may improve the tolerability of PDT and the efficacy rate of field therapy in organ transplant recipients. One study demonstrated the superiority of this combination therapy in a population of 16 organ transplant recipients on immunosuppressants with at least 2 moderate to severely thick AKs in each of 4 comparable areas in the same anatomic region.[9] The 4 areas were randomized to a single session of AFXL-dPDT, dPDT alone, conventional PDT, or AFXL alone. Ablation was performed with a fractional Er:YAG laser. The AFXL-dPDT and dPDT alone groups received MAL for 2.5 hours without occlusion, and the conventional PDT group received MAL for 3 hours with occlusion. Daylight exposure in dPDT groups was initiated 30 minutes after MAL application for 2 hours total. A baseline total of 542 AKs were treated. At 3-month follow-up, the complete response rate was highest for the AFXL-dPDT group (74%) compared to dPDT alone (46%; P=.0262), conventional PDT (50%; P=.042), and AFXL alone (5%; P=.004). Pain scores for AFXL–dPDT and dPDT alone were significantly lower than for conventional PDT and AFXL alone (P<.001).[9]

Nonablative Lasers

By heating the dermis to induce neogenesis without destruction, nonablative lasers offer superior healing times compared to their ablative counterparts. Multiple treatments with nonablative lasers may be necessary for maximal effect. Four nonablative laser devices have demonstrated efficacy in the treatment of multiple AKs[10-14]: (1) the Q-switched 1064-nm Nd:YAG laser, with or without a 532-nm potassium titanyl phosphate (KTP) laser; (2) the 1540-nm fractional erbium glass laser; (3) the 1550-nm fractional erbium-doped fiber laser; and (4) the 1927-nm fractional thulium laser (Table 3).

In a proof-of-concept study of the Q-switched Nd:YAG laser with the 532-nm KTP laser, 1 treatment session induced full remission of AKs in 10 patients at follow-up day 20, although the investigator did not grade improvement on a numerical scale.[10] In a study of the fractional Q-switched 1064-nm Nd:YAG laser alone, 6 patients with trace or mild AKs received 4 treatment sessions at approximately 2-week intervals.[14] All but 1 patient (who had trace AKs) had no AKs at 3-month follow-up.

The efficacy of the 1540-nm fractional erbium glass laser was examined in 17 participants with investigator-rated moderate-to-severe AK involvement of the scalp and face.[12] Participants were given 2 or 3 treatment sessions at 3- to 4-week intervals and were graded by blinded dermatologists on a quartile scale of 0 (no improvement), 1 (1%–25% improvement), 2 (26%–50% improvement), 3 (51%–75% improvement), or 4 (76%–100% improvement). At 3 months posttreatment, the average grade of improvement was 3.4.[12]

The 1550-nm fractional erbium-doped fiber laser was tested in 14 men with multiple facial AKs (range, 9–44 AKs [mean, 22.1 AKs]).[11] Participants received 5 treatment sessions at 2- to 4-week intervals, with majority energies used at 70 MJ and treatment level 11. The mean AK count was reduced significantly by 73.1%, 66.2%, and 55.6% at 1-, 3-, and 6-month follow-up, respectively (P<.001).[11]

The 1927-nm fractional thulium laser showed promising results in 24 participants with facial AKs.[13] Participants received up to 4 treatment sessions at intervals from 2 to 6 weeks at the investigators' discretion. At baseline, patients had an average of 14.04 facial AKs. At 1-, 3-, and 6-month follow-up, participants exhibited 91.3%, 87.3%, and 86.6% reduction in AK counts, respectively. The mean AK count at 3-month follow-up was 1.88.[13]

Due to limited sample sizes and/or lack of quantifiable results and controls in these studies, more studies are needed to fully elucidate the role of nonablative lasers in the treatment of AK.

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TABLE 3. Nonablative Lasers as Monotherapy for AK Field Treatment

Reference (Year)	Laser	No. of Participants	Laser settings	Results	Adverse Effects
Demetriou[10] (2011)	Q-switched 1064-nm Nd:YAG laser/532-nm KTP laser	10	(1) 1064 nm Nd:YAG (400–700 pulses; 400 MJ), (2) 532-nm KTP (pulses varied; 200 MJ)	Full remission for all participants	Erythema
Katz et al[11] (2011)	1550-nm fractional erbium-doped fiber laser	14 (3 lost to follow-up)	Energy: 20–70 MJ; Treatment level: 32%–40% coverage; No. of passes: 8–10	73.1% AK reduction at 1-mo follow-up; 66.2% at 3 mo; 55.6% at 6 mo ($P<.001$)	Pain (1 patient withdrew due to pain); pain scores ranged from 2–9 (on a scale of 1 to 10); mild erythema and edema
Lapidoth et al[12] (2013)	1540-nm fractional erbium glass laser	17	Fluence: 75 MJ/microbeams; Density: 100 microbeams/cm^2; Pulse duration: 15 ms; No. of passes: 2–3	3.4 grade of improvement on 4-point grading scale (grade 3, 51%–75% improvement; grade 4, 76%–100% improvement)	Erythema, edema, crusting, erosions, superficial ulceration, discomfort
Weiss et a[13] (2013)	1927-nm fractional thulium laser	24	Fluence: 5–20 MJ/cm^2; Treatment level: 40%–70% coverage	91.3% AK reduction at 1-mo follow-up; 87.3% at 3 mo; 86.6% at 6 mo	Moderate erythema, mild edema
Gold et al[14] (2014)	Fractional Q-switched 1064-nm Nd:YAG laser	6	Energy: 400–1200 MJ; Density: 6–13 J/cm^2	No AKs (n=5); trace AKs (n=1)	Erythema, pain

Abbreviations: AK, actinic keratosis; KTP, potassium titanyl phosphate.

Future Directions

Iontophoresis involves the noninvasive induction of an electrical current to facilitate ion movement through the skin and may be a novel method to boost the efficacy of current field therapies. In the first known study of its kisnd, iontophoresis-assisted AFXL-PDT was found to be noninferior to conventional AFXL-PDT[15]; however, additional studies demonstrating its superiority are needed before more widespread clinical use is considered.

Pretreatment with AFXL prior to topical field-directed therapies also has been proposed.[16] In a case series of 13 patients, combination therapy with AFXL and ingenol mebutate was shown to be superior to ingenol mebutate alone (AK clearance rate, 89.2% vs 72.1%, respectively; $P<.001$).[16] Randomized studies with longer follow-up time are needed.

Conclusion

Ablative and nonablative laser systems have yielded limited data about their potential as monotherapies for treatment of multiple AKs and are unlikely to replace topical agents and PDT as a first-line modality in field-directed treatment at this time. More studies with a larger number of participants and long-term follow-up are needed for further clarification of efficacy, safety, and clinical feasibility. Nevertheless, fractional ablative lasers in combination with PDT have shown robust efficacy and a favorable safety profile for treatment of multiple AKs.[6-9] Further, this combination therapy exhibited a superior clearance rate and lower lesion recurrence in organ transplant recipients—a demographic that classically is difficult to treat.[6-9]

With continued rapid evolution of laser systems and more widespread use in dermatology, monotherapy and combination therapy may offer a dynamic new option in field cancerization that can decrease disease burden and treatment frequency.

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