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# Innovative Therapy of CTCL: Beyond PUVA and Nitrogen Mustard

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## Synopsis

Cutaneous T Cell Lymphoma is a malignancy of skin homing T cells. This unique population of lymphocytes requires alternative therapies than those used in nodal lymphomas. Although phototherapy and nitrogen mustard have been standard treatments for decades, newer therapies have been arriving with increased frequency. Moreover some therapies, currently used to treat other disease, have been used in CTCL with good effect. These innovative therapies in CTCL are discussed, with review of current data and examples of how these therapies may be utilized today.

### Keywords

Mycosis Fungoides; Cutaneous T-Cell Lymphoma; Therapeutics; Phototherapy; Laser; Imiquimod

## Introduction

The incidence of cutaneous T-cell lymphoma (CTCL) in the United States continues to rise. [1] Although CTCL has come to encompass a broad group of cutaneous lymphomas, mycosis fungoides and Sezary syndrome remain the most common forms of CTCL. The staging system for CTCL applies only to mycosis fungoides and Sezary syndrome (MF/SS). [2–3] Additionally, most of the literature on therapy and the treatments discussed in this paper are focused on these variants. As the number of patients with MF/SS increases so do the therapy problems that arise in their management.

There are two dichotomies that must help position available treatments. (see Table 1) One is whether the treatment is localized or generalized. The second is whether the goal of therapy is to achieve remission or to achieve palliation. The initial therapies published with MF/SS would be considered as generalized and with intent to remit: topical nitrogen mustard and photochemotherapy with psoralen and ultraviolet A light. Nitrogen mustard was first applied



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topically to MF in 1959. [4] Perhaps the most widely used generalized remittive therapy, phototherapy, has been in use for treatment of the disease since the 1970s. [5] Undoubtedly the highest response rates for remission are with radiotherapy whether generalized (total skin electron beam [6]) or localized [7]. While the use of NM and PUVA has remained stable, there has been an expansion in the variety of therapies in the categories of localized ablative, generalized palliative, and generalized remittive (as outlined in Table 1). When lesions do not therapeutically respond to the first course of conventional therapy then the innovative new therapies need to be considered. This review discusses some innovative therapies that are being used to treat MF/SS. While randomized controlled trials are needed to verify the preliminary results, a patient's predicament may benefit from the promising therapies reviewed.

## Localized Ablative Therapies

### Photodynamic Therapy

Photosensitizers in phototchemotherapy have been used to treat skin disease for centuries. The use of psoralen with ultraviolet light has been a key strategy in the treatment of MF for decades. With the application of, photodynamic therapy (PDT), which utilizes aminolevulinic acid (ALA) and its derivatives in the presence of light, a new topical photosensitizing strategy has been used for the treatment of cutaneous malignancies. [8] Topical PDT is activated in the visible light spectrum (580–720 nm). The specificity for PDT is still under investigation but it is known that only cells within the epidermis and epidermal appendages initially become photoreactive. Interestingly, tumors of epidermal origin are also photosensitive, even when located within the dermis, suggesting that the depth of ALA absorption or light penetration are not the only factors determining which cells may be targeted by this treatment. [9] Activated T lymphocytes, as observed in skin lymphoma, can absorb ALA, whereas unactivated T lymphocytes do not. [10] Therefore, the use of PDT in mycosis fungoides has a physiologic basis. Malignant T cells localized in plaques or tumors of CTCL can be bathed in ALA and thereafter photoactivated, causing cell death through the production of reactive oxygen species and apoptosis.

The use of PDT in CTCL dates back to 1994 when Svanberg and Wolf both described patients with CTCL treated with PDT. Svanberg treated two patients, once or twice for a year or less, showing a complete response. [11] Wolf also reported complete remission in two patients with 4 to 5 courses of PDT over 6 months. [12] Later Oreinstein treated one patient with tumor stage MF who showed a complete response confirmed by biopsy with 2 years of follow-up. [13] In 2001, a larger case series was performed which showed the first histologic confirmation of clearance of MF with PDT. [14] Ten patients with mycosis fungoides, 8 with plaque stage and 2 with tumor stage, were treated. They had all failed previous therapies including etretinate, PUVA, and radiotherapy. In lesions that showed a clinical response to PDT, there was a decrease in CD3+ CD4+ cells in the epidermis and dermis although a few foci remained. In a patient that did not respond, a longer incubation time with the ALA (18 hours instead of 5–6 hours), did not change the clinical or histologic appearance of the lesions after two treatments. The patient who had previously received radiotherapy had some baseline fibrosis and required 11 cycles of treatment in order to respond.

Various forms of ALA and various light sources have been used. (See Table 2) There have been over 30 patients reported and the results have been favorable. Because there has been no consistency in methodology, response rates cannot be obtained, however multiple studies have shown response in both plaques and tumors of MF. Although recurrence may occur, there were many remissions that lasted at least one to two years during follow-up. Application time varied but most studies used a range of 3–6 hours. Light sources have also

been variable although all were within the visible light spectrum. The various light sources, doses, and dose rate used in photodynamic therapy have been reviewed elsewhere and those used in cutaneous T cell lymphoma are shown in Table 2. [15] For lesions of cutaneous T cell lymphoma that are refractory to standard therapies, PDT is an emerging therapy with an extensive history awaiting further exploration.

## When to consider

- Oligolesional persistent disease
- Patients where a radiation sparing therapy is needed due to prior sun, phototherapy or radiotherapy

### Cryotherapy

Cryosurgery is readily available and an overlooked modality in treating cutaneous T cell lymphoma. The freeze-thaw cycle causes localized tissue injury that can destroy all living cells, leading to necrosis. [16] Freezing should be fast and thawing should be slow. Most dermatologists use cyrotherapy for the treatment of benign and pre-malignant lesions, including warts and actinic keratoses and less commonly to treat malignancy. Nevertheless, there is little evidence in the medical literature to direct the physician as to the exact procedural method. This is especially true for treating malignant T cells. There has been no study showing the optimal temperature for killing lymphocytes in human skin. Nevertheless, there is little doubt that cryotherapy can be used to destroy both benign and malignant cells in the skin, including T cells.

In general most experts report that multiple freezes are better for malignant lesions than a single freeze- thaw cycle. [16] It can be used to treat any part of the body, so is particularly useful for small lesions that have resisted previous therapies. As with other malignancies, a greater amount of necrosis is required to destroy a malignant lesion. [17] A tissue temperature of −50 to −60°C will destroy malignant lesions. [16] Because the depth of damage is determined by the freeze time, thaw time and area treated, experience is needed to properly deliver the cryogen. However, malignant lymphocytes in the skin, even when within a tumor, can be readily killed with freezing. One guide is to choose a thaw time that is at least twice the freeze time. Although a lateral margin of normal skin should be treated, there is no data regarding its size. Topical and injected anesthetics can be used for treating larger lesions.

Patients with cutaneous T cell lymphoma who are treated with cryosurgery have a typical tissue reaction that includes crusting and occasionally bulla formation. Weeping and sloughing of the skin are also common. Melanocytes are more sensitive to freezing than most other cell types in the skin, and therefore, patients should be warned about possible hypo- and depigmentation after treating the malignant lesion. As mentioned, although it has not been established in all cell types, destruction of malignant cells often requires colder temperatures. Therefore, the use of higher temperatures to protect melanocytes may ultimately lead to failure in adequately treating the malignancy.

## When to consider

- Oligolesional persistent disease
- Patients where a radiation sparing therapy is needed due to prior sun, phototherapy or radiotherapy

### Surgery

Surgery with steel can be an overlooked modality in treating cutaneous T cell lymphoma. Although commonly used in the treatment of cutaneous B cell lymphoma, the use of primary excision in T cell lymphoma is infrequent. [18] There have been reports of treating variants of MF including unilesional MF with surgical excision. [19] Case reports in the literature have suggested that lesions do not recur. [20] It is more natural to consider surgical excision in a patient presenting with one small lesion. However, surgical excision should also be considered as an option in patients who have failed first line therapies or have had a recurrence or non- response to treatment of a solitary lesion.

## When to consider

- Patients with unilesional mycosis fungoides, pagetoid reticulosis, or small, solitary recurrent lesions.

### Excimer Laser

The FDA approval of the excimer laser for psoriasis and vitiligo has increased access to this therapeutic option. The xenon-chloride laser emits monochromatic light in the ultraviolet range at a wavelength of 308-nm. This wavelength is within the ultraviolet B spectrum (320nm–280nm) which therefore suggests that the excimer laser light would be effective in MF. There have been a number of case reports/series and open trials showing benefit. It has a safety profile similar to phototherapy as local phototoxicity is the major adverse event. However the ability to localize treatment to lesional skin helps minimize this.

Nastico, et. al. treated five patients with Stage IA patch/plaque MF and 10 lesions in total with excimer laser in 2004 with one year of follow-up. [21] All 10 lesions had a complete response without recurrence over one year. (See Table 3) Five patients with patch/plaque disease were treated by Passeron, with all showing a clinical response and 4 of 5 showing complete response. [22] At the end of the trial all 5 had maintained the response, including the partial responder who had “minimal residual activity”. Mori, et. al. also presented a case series in four patients with Stage IA disease. [23] Seven lesions were treated and showed complete response with follow-up between 3 and 28 months. One patient developed a new lesion in a different, untreated site during follow-up while the other three remained disease free. In one case series of two patients, recurrence of MF after excimer laser was observed. The patient had patch/plaque disease and previously developed recurrence following a complete response with PUVA 15 months prior. [24] Because the patient had previously experienced nausea with psoralen, after disease recurrence excimer laser was utilized. Several lesions showed a partial or complete response, but she continued to develop new plaques after discontinuation of therapy. Lastly two patients have been presented who had individual lesions treated with excimer laser while also undergoing narrow-band ultraviolet light therapy for other lesions. [25] One patient had a complete response of both NB-UVB and excimer laser treated lesions. The other patient had a partial and incomplete response to her lesions with both NB-UVB and excimer laser.

## When to consider

- In patients with unilesional MF. Especially those patients that have had good success with phototherapy or have not used phototherapy.
- This would be a good modality for a patient successfully treated with phototherapy that has sanctuary lesions that are not well exposed during ultraviolet treatments such as those on the feet, inguinal area, or parts of the face.

### Imiquimod

Imiquimod is a nucleoside analog and agonist of Toll Like Receptor (TLR) 7 and 8. It was originally developed while looking for antiviral drugs, however it does not have direct antiviral properties. Imiquimod does stimulate the release of interferon and cytokines which have both antiviral as well as antitumoral responses. [26–27] The exact mechanism behind the antitumoral response is still unknown; however there are a several possibilities including activation of innate immunity as well as the stimulation of dendritic cells which directs a cell-mediated antitumor response may be important. [28] The central role of the transcription factor NF-kappa B also requires further exploration as it mediates Toll Like Receptor signalling. Lastly because CTCL is generally composed of Th2 T lymphocytes, the production of interferon correcting the Th1 and Th2 imbalance may be important in the treatment of CTCL.

Although larger clinical trials are needed, there is mounting evidence from case reports and series that imiquimod has activity against CTCL. (See Table 4) One current limitation in the United States is that the cream is distributed in small packets, which are difficult to use over larger areas of the body. A recent review of the currently published cases has shown imiquimod has been applied with good success at many centers. In Rook's initial report, the cream was applied daily, which led to the patient having redness, vesiculation, erosion and pruritus of the lesion. This led to a 2 day discontinuation of treatment, but the patient was then able to restart daily application. The inflammation decreased gradually over the 4 month course of treatment. [29] Deeths reported a case series of 6 patients, who were allowed to continue photochemotherapy or interferon during imiquimod treatment. [30] This trial also allowed patients to decrease frequency of dosing to once a week if they experienced irritation with 3 times weekly application. Despite the decreased frequency, 4 of 6 patients experienced some localized irritation, including one patient with ulceration and suspected cellulitis requiring oral antibiotic therapy.

Two studies have shown synergy of imiquimod with systemic interferon. [30–31] Imiquimod has been used to treat unilesional MF on the penis and buttock. [32–33] In most case reports to date, the patient had failed at least one standard first line topical therapy, suggesting imiquimod may be beneficial in treatment resistant MF. Recently Coors obtained a complete response with imiquimod in one patient with CD30+ anaplastic large cell lymphoma (ALCL), suggesting that imiquimod may have applicability beyond mycosis funoides. [34] Didona has also examined imiquimod in three patients with ALCL with complete response. [35] Martinez-Gonzalez reported 4 patients treated with imiquimod showing a complete response. However during the study period, one patient developed new lesions outside of the treatment area. [31]

There is ample data supporting the effect of imiquimod in certain patients with MF. Larger studies will provide better efficacy data, but the 20 patients that have been reported thus far, show some level of activity. One important question will be whether imiquimod can provide long term remission. It is always important to consider this when choosing therapies in CTCL as some treatments provide temporary responses but do not provide solid remissions. For example, plaques of MF will disappear after treatment with ultrapotent topical corticosteroids, however experience shows that many of these patients have recurrence or new lesions. On the other hand, photochemotherapy can provide long(er) term remissions and is generally a preferred therapy when looking for such remission compared to topical corticosteroids. It will be important to determine if imiquimod can provide long term remission.

Lastly the studies reported to date included patients who had failed more standard therapies such as topical carmustine and nitrogen mustard, topical corticosteroid, systemic interferon,

PUVA, low-dose retinoids, and radiation. With the positive response to date, there is data to support imiquimod for the topical treatment of localized MF that has failed standard therapies.

## When To Consider

- Patients who have failed topical corticosteroid, bexarotene gel, nitrogen mustard/ carmustine, or phototherapy yet have residual or new isolated plaques.
- Patients with plaques, genital lesions or unilesional MF.

## Generalized Therapy for Palliation

### Romidepsin

Many of the modalities currently approved for CTCL are primarily palliative: denileukin diftitox, oral bexarotene, and oral vorinostat. Any systemic therapy that has its success determined by quality of life indices must have an acceptable level of side effects. With CTCL, there can be improvement of disease utilizing drugs that inhibit histone deacetylase. The recently approved romidepsin, provides an innovative approach to HDAC inhibition with a weekly pulsing regimen that is relatively free of severe adverse events. [36] Less than half of the patients achieved a significant response but those who did had a marked reduction in pruritus. The side effect profile was markedly similar to the oral HDAC inhibitor vorinostat. Many patients had mild gastrointestinal upset, mild asthenia and anorexia. The most common laboratory abnormality was bone marrow suppression that was mild. As with vorinostat, the elctrocardiographic changes of romidepsin can be striking but appear to be inconsequential. [37]

## Generalized Therapy for Remission

### Stem Cell Transplant

Although the number of patients treated with stem cell transplantation remains small, there are a number of centers throughout the United States which have experience with transplantation in CTCL. Reduced-intensity allogeneic stem cell transplants cause less immunosuppression while still allowing for a graft versus lymphoma response. Reduced-intensity allogeneic stem cell transplants have been performed with increasing frequency in all lymphomas and have made their way into use for CTCL. There is less morbidity associated with the reduced conditioning treatment and therefore it allows for older patients and those who are less fit to be considered for transplant. Both allogeneic and autologous stem cell transplants have recently been reviewed elsewhere. [38]

Allogeneic stem cell transplants have shown better success, however there is an increased morbidity associated with the procedure. Of 21 patients treated to date with allogeneic SCT, 15 were reported alive without evidence of disease at variable follow-up times. Although standard intensity regimens were initially utilized, more recently reduced-intensity regimens have been used. Both have shown good success. Although the number of reported transplants for CTCL remains low, there have been complete, durable responses in patients who have failed standard therapies and who have the most aggressive disease.

## When to Consider

- Aggressive disease such as transformed MF, lymph node involvement, erythroderma, or widespread tumors
- Patients under the age of 70, especially with sibling donors

## Conclusion

The treatment modalities available to treat cutaneous T cell lymphoma have been expanding in recent years. Targeted biologic therapies, molecular targets that cause T lymphocyte apoptosis, and new application of established therapies, have allowed for a greater armamentarium in treating CTCL. Moreover as we develop better biomarkers for the disease, we will be able to predict whether a particular patient will respond to a particular treatment modality.

However for patients currently suffering from CTCL, treatments are required today. There are a number of moderately effective standard therapies for CTCL. Nevertheless failures are common. Moreover, partial responses are common and these require additional therapy. We have described a number of available therapies that can be used strategically to treat CTCL. In some cases, such as excimer laser or imiquimod, the therapy has a well understood safety profile and can be helpful for recalcitrant patch-plaque MF. In others, such as photodynamic therapy, excision, and cryotherapy, the treatment can be used not only for patch-plaque stage disease, but also for limited tumor stage disease. Lastly stem cell transplant has a role in treating patients with advanced stage disease who have failed at least one standard therapy and who have a health status and age which would allow stem cell transplant. The therapies presented here are the most recent ones to join the ranks of treatments listed in Table 1. New therapies will still employ old strategies of remission or palliation. As these therapies are considered, their success will be determined by improvement in the quality of life or the ability to induce durable remissions. Both of these goals represent significant impacts that the treating physician can have when managing MF/SS.

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## Table 1

The two dichotomies that help position therapies are based on properties of the therapy. One is whether the therapy is localized or generalized. The latter includes both systemic and total skin treatments. The second property is whether the treatment is administered with a primary intent of reducing tumor burden to zero (remittive) or whether it is to improve quality of life (palliative). While there have been infrequent remissions with some of the palliative therapies, a cut off of 50% remission rate was used to define the treatments in the far right column.

| | **Palliative** | **Remittive** |
|---|---|---|
| Localized | Steroid Cream | X-ray<br>Bexarotene Gel<br>Excimer Laser<br>Imiquimod<br>Cryotherapy<br>Surgical Excision |
| Generalized | Prednisone<br>Chlorambucil<br>Methotrexate<br>Photopheresis<br>Oral Bexarotene<br>Oral Vorinostat<br>Denileukin Diftitox<br>Romidepsin<br>Liposomal Doxorubicin<br>Alemtuzimab | Nitrogen Mustard<br>Total Skin Electron Beam<br>Phototherapy<br>Allogeneic Stem Cell Transplantation |

**Table 2**

Photodynamic Therapy

| | Photosensitizer | Application time (hours) | Source | Dose(J $cm^{-2}$) | Follow-Up (months) | Patients |
|---|---|---|---|---|---|---|
| Wolf, 1994 [20] | 20% dALA | 4–6 | Modified Slide Projector | 40 | 8 to 14 | 2 |
| Svanberg, 1994 [11] | 20% dALA | 5 to 18 | Doubled Pulsed Frequency Nd:YAG dye laser | 60 | 6 to 14 | 2 |
| Orenstein, 2000 [13] | 20% dALA | 16 | Broad Band Red Light (580–720nm) | 170 to 380 | 24 to 27 | 2 |
| Edstroem, 2001 [14] | 20% dALA | 5–6 | Waldmann PDT 1200 (600–730nm) | 50 to 180 | 4 to 21 | 10 |
| Markham, 2001 [39] | 20% dALA | 4 | Waldmann PDT 1200 | 20 | 12 | 1 |
| Paech, 2002 [40] | 20% dALA | 4 | Waldmann PDT 1200 | 180 | 12 | 1 |
| Leman, 2002 [41] | 20% dALA | 6 to 24 | Xenon short arc discharge lamp | 100 | 12 | 1 |
| Coors, 2004 [42] | 20% dALA | 6 | Waldmann PDT 1200 | 96 to 144 | 14 to 18 | 4 |
| Umegaki, 2004 [43] | 20% dALA | 6 | SUS66 illuminator | 120 | NR | 1 |
| Zane, 2006 [44] | 20% mALA | 3 | Aktilite CL128 Lamp | 37.5 | 12 to 34 | 5 |
| Recio, 2008 [45] | 20% ALA | 4 | 585nm Pulsed Dye Laser | 8 | 24 | 2 |
| Hegyi, 2008 [46] | 20% mALA | 3 | Aktilite lamp (635 nm red light) | 100* | 16 | 1 |

*200 J $cm^{-2}$ caused ulceration,

NR- Not reported.

**Table 3**

Excimer Laser Therapy

| | Starting Dose (J cm$^{-2}$) | Further Dosing (J cm$^{-2}$) | Frequency | Treatments | MED testing | Follow-Up (months) | Patients | Side Effects | Recurrence | Complete response |
|---|---|---|---|---|---|---|---|---|---|---|
| Nistico, 2004 [21] | 0.5–1 (Twice MED) | 0.15–0.5/ session | q 7 to 10 d | 10 | Yes | 12 | 5 | Transient hyperpigmentation, itch | None | 5 |
| Passeron, 2004 [22] | 0.17–0.5 (50mJ below MED) | 0.1/per week | Twice weekly | 21 | Yes | 3 | 5 | Erythema, blistering, | None | 5 |
| Mori, 2004 [23] | 0.5–1 (2–3 time MED) | 0.15–0.5/ session | Weekly | 8 | Yes | 28 | 4 | Erythema, itch | None | 3 of 4 |
| Meisenheimer, 2006 [24] | 0.1–0.15 | 0.3/session | Twice weekly | 14 to >38 | Yes | 6 | 2 | Persistent Erythema | 1 of 2 | 1 of 2 |
| Kontos, 2006 [25] | NR | NR | Thrice weekly | 14 to 22 | NR | NR | 2 | Erythema, itch, blisters, eroisions, hyperpigmentation | 1 of 2 | 1 of 2 |

NR- Not Reported

**Table 4**

Imiquimod Therapy

| | Stage | Patients | Length of Treatment | Frequency | Response | Side Effects | Recurrence | F/U |
|---|---|---|---|---|---|---|---|---|
| Suchin, 2002 [29] | IA | 1 | 4 months | Daily | CR | Vesicles, erythema, erosions, pruritus | NR | 4 months |
| Dummer, 2003 [47] | NR | 1 | 8 weeks | Daily | CR | Ulceration | No | 12 months |
| Chong, 2004 [48] | IB | 3 | NR | Daily | NR | Mild Irritation | NR | 32 weeks |
| Deeths, 2005 [30] | IA to IIB | 6 | 12 weeks | 1–3 times per week | 3 of 6 had CR, 1 of 6 had PR, 2 of 6 had minimal or no response | Erythema, irritation, erosion and ulceration | NR | 16 weeks to 2 years |
| Chiam, 2006 [33] | IA | 1 | 4.5 months | Every other day | CCR | Pain, ulceration | No | 6 mo |
| Ardigo, 2006 [32] | IA | 1 | 24 weeks | 5x/week | CR | Erythema, Edema | No | 6 mo |
| Coors, 2006 [34] | IA to IB | 4 | 8–24 weeks | 3x/week | 50% CCR | Erythema, papules, pruritus | NR | 6 to 45months |
| Martinez-Gonzalez, 2008 [31] | IA to IIB | 4 | 3–14 months | 3x/week | 100% CR | Localized inflammation | Yes | NR |

CR- Complete Response, CCR-Clinical Complete Response (no histologic confirmation), PR- Parital Response, NR- Not Reported.