

## Photopheresis Therapy of Cutaneous T-Cell Lymphoma: The Yale-New Haven Hospital Experience

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Over the past two years, the photopheresis treatment program at Yale-New Haven Hospital has treated 32 patients with cutaneous T-cell lymphoma. There were 19 erythrodermic patients who had photopheresis as their first systemic therapy. Five of these cleared 75 percent of their skin and the majority of erythrodermics achieved an improved quality of life. Those with best responses were treated earlier in the course of their disease and had more normal proportions of CD4 and CD8 subsets when compared to patients with poor responses. In addition, patients with tumor stage disease and those patients in relapse after intensive radio- and chemotherapy were treated with photopheresis. These results demonstrate that photopheresis has a role in the management of cutaneous T-cell lymphoma.

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Extracorporeal photochemotherapy (photopheresis) was initially reported in 1987 to produce clinical improvement in a majority of patients with erythrodermic cutaneous T-cell lymphoma [1]. That report consisted of a multi-center clinical trial, with patients being treated for a minimum of one year. Roughly one-fourth of erythrodermic patients went into remission, and one-fourth did not improve significantly. The remaining patients achieved a marked improvement in skin condition and quality of life but still had demonstrable CTCL.

At the time of the clinical trial, patients were treated with the UVAR I instrument, which had a treatment time of six to seven hours. Since the completion of the trial, the UVAR II system, with its treatment time of three to four hours, has been used. In this report, we present the results of using the UVAR II system in patients with cutaneous T-cell lymphoma (CTCL).

The results of this treatment in the management of erythrodermic patients are discussed in comparison to the initial clinical trial. In addition, patients with tumor state disease have had photopheresis incorporated into their treatment regimens with promising results.

### PATIENT POPULATION

During the first two years of operation, the photopheresis program at Yale-New Haven Hospital entered a total of 32 CTCL patients on to treatment for a minimum of six months each. The patients ranged in age from 39 to 77. There were three distinct

TABLE 1  
Stratification of Patients Treated with Photopheresis at Yale–New Haven  
Hospital

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Three categories of CTCL patients	
1. Erythroderma	19 with extracorporeal photochemotherapy as first systemic Rx 3 after chemotherapy
2. Tumor Stage Disease	2 without radiation Rx 2 with spot therapy of tumors 2 cleared by 3,600 rads E beam 3 in relapse after beam/chemotherapy
3. Widespread Disease After Beam/Chemotherapy	3 in relapse > 1 year

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clinical groups: erythroderma, tumor stage, and those with widespread disease in relapse for more than one year after multi-modality therapy. As shown in Table 1, the patients represent a variety of stages of CTCL. The majority of patients were those with erythroderma receiving photopheresis as their first line of therapy. Skin involvement by the disease was assessed by examining each patient when they presented for treatment. Skin involvement of a particular region was graded on a 0 to 4 scale as done in conjunction with the initial clinical trial [1]. Surface involvement is thus graded according to the percentage of surface involved and degree (0 to 4) to which that area is involved. Responses are graded into three categories: patients clearing either 75 percent of their surface involvement, patients involving more than 25 percent of their involvement but less than 75 percent, and those with less than 25 percent involvement.

### LABORATORY STUDIES

The diagnosis of CTCL was made histologically in all cases. The determination of peripheral blood lymphocyte surface markers utilized flow cytometry with antibodies to CD3, CD4, and BE-2 [2]. The method for measuring 8-methoxypsoralen (8-MOP) levels was that of Gasparro et al. [3], and these measurements were performed in the Yale Photobiology Laboratory.

### PHOTOPHERESIS

Photopheresis therapy was performed by having patients ingest .6 mg/kg 8-methoxypsoralen. A 16-gauge catheter was placed in an antecubital vein and blood separated on a discontinuous centrifuge with collection of buffy coat cells. After 240 cc of buffy coat had been collected, the leukocyte-rich fraction was then diluted with 200 cc saline and 200 cc plasma. The buffy coat is then irradiated by ultraviolet A light (UVA)-emitting bulbs. The irradiation commenced with the initial collection of buffy coat; the latter feature constitutes the major difference between the UVAR I and UVAR II instruments. The former machine did not start irradiation until all buffy coat collection was complete, so that the total treatment time was decreased with the second-generation unit.

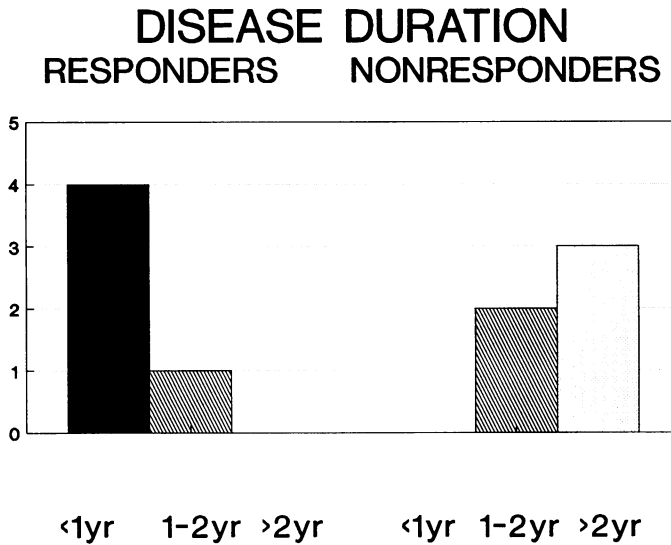


FIG. 1. A comparison of the five best responders to the five least responders shows that best responses occurred when therapy was initiated earlier in the course of the disease. The time intervals are the time from disease onset to commencement of photopheresis.

### TREATMENT REGIMENS

Patients were initially treated for two consecutive days at every-four-week intervals. Treatments were conducted at the bedside during a three-day hospitalization; this regimen was maintained for six months. After six months, a clinical evaluation was performed. Those demonstrating marked clinical improvement were maintained on the four-weekly treatment schedule. Their treatments would be continued until maximum clearing appeared. An additional six months of therapy after this point was administered to insure the stability of the response. Once stable for this additional six months, patients are then gradually tapered by adding one week per cycle every three cycles. After this schedule has been extended to one cycle of therapy every eight weeks for three times, their therapy is stopped.

Adjunctive therapy was considered for patients with responses that were incomplete. Methotrexate adjunctive therapy consisted of an initial dose of 15 mg between treatment cycles. If this dosage was well tolerated, the dose was advanced to weekly, with no dosing within seven days before or after a cycle of photopheresis. Azathioprine adjunct was initiated at 100 mg/day. Nitrogen mustard was utilized at 10 mg percent concentration in Aquaphor. Total body electron beam therapy was administered as described in previous studies from this institution [4]. A total dose of 3,600 rads was given in 36 sessions.

### RESULTS

#### *Erythroderma*

Twenty-two patients with erythroderma were treated. Nineteen of these had photopheresis as the first line of therapy. The beneficial response appeared on the head and upper trunk first, with a decrease in erythroderma and scaling. As the erythroderma improved in a cephalocaudal manner, patients had less chills and edema. Pruritis and palmo-plantar involvement tended to be the last areas to resolve. Five of

## CD4 AND CD8

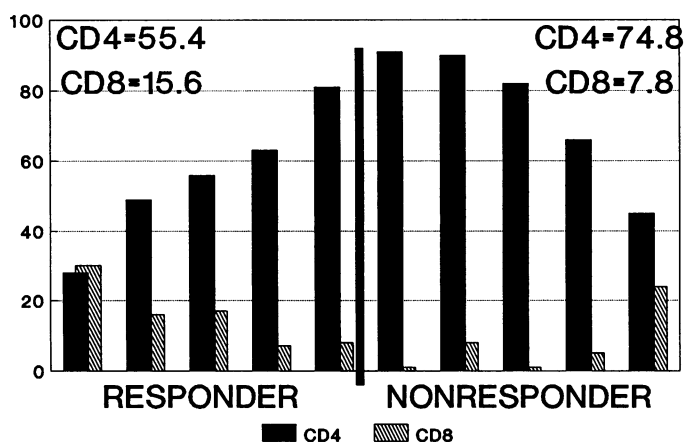


FIG. 2. A comparison of CD4 and CD8 peripheral blood lymphocyte subsets in the best responders and the five least responders. The CD4 and CD8 values expressed are mean values. The mean values of the CD4/CD8 ratios are 5.27 for responders, 39.6 for non-responders.

the patients cleared over 75 percent of their skin involvement. Ten patients cleared 25 to 75 percent, while four patients had less than 25 percent improvement.

### *Features of Responders and Non-Responders*

The five patients with greatest therapeutic response were compared to the five with the smallest response. Two features characterized the responding group (see Figs. 1 and 2). Patients in the most responsive group had mean CD4, CD8, and 4/8 ratios of 55.4, 15.6, and 5.27, respectively. In comparison, the CD4, CD8, and 4/8 ratios of the least responsive group were 74.8, 7.8, and 39.6. Another feature which characterized the responsive group was the shorter interval between onset of disease and the start of photopheresis (see Fig. 1).

### *Adjunctive Therapy*

For those patients in the intermediate response group, adjunctive therapy has the potential of working with photopheresis to lead to a greater improvement of the disease. Patients considered for adjunctive therapy had erythroderma with a stable but not acceptable improvement in response to photopheresis. Repeat skin biopsies were performed to demonstrate disease and to ensure that the patient had not developed tumor or plaque stage, which would dictate a change in therapy overall.

In eight patients, the test dose of 15 mg methotrexate between two cycles of photopheresis (two weeks after one cycle and before the other), was well tolerated. All eight patients were advanced to the schedule of three doses between treatments. Of these patients, two had previously begun oral daily prednisone (40 mg/day) to improve flares of their disease. Prednisone was begun at 40 mg per day for two weeks, then decreased to 30 mg per day for one week, and 20 mg per day for one week. After a four-week course, attempts were then made to taper to 5 mg per week. Any return of disease activity returned the prednisone dose to 20 mg, and attempts to taper were re-started after addition of adjunctive therapy. When the prednisone could not be successfully tapered, the methotrexate was initiated. Cessation of prednisone was achieved within two months of methotrexate, and in both patients an improved clinical status appeared and stabilized. The total time on prednisone was five months and three

and a half months for these two patients. In the other six patients, methotrexate led to a complete remission in one, greater than 50 percent clearing in two, and a stabilized pattern in three. The adjunctive use of steroids in photopheresis is best utilized for symptomatic short-term management. All patients had been weaned to an oral prednisone dose of 20 mg every other day or less prior to starting photopheresis. Topical steroids were initiated with .05 percent hydrocortisone in Aquaphor. If pruritus did not improve and the patient had received a minimum of six cycles of photopheresis, there would be a trial of 0.1 percent triamcinolone applied at night. If this treatment were unsuccessful, a one-month trial of nightly halcinonide (Halog) applications would be attempted. One patient required two months of halcinonide, but otherwise these agents were used sparingly.

Azathioprine therapy was initiated in three patients. In one, it was instituted to facilitate the tapering of that patient's prednisone dose but was unsuccessful; thus the azathioprine was discontinued after two months. One patient who commenced photopheresis with a white blood cell count of over 50,000 cells/mm<sup>3</sup> had azathioprine initiated at the start to help lower this elevated white blood cell count. Over 18 months, his azathioprine dose was 100 mg per day, and the patient gradually improved. After the white blood cell count decreased to <12,000, the azathioprine was discontinued, and the patient has maintained a white blood cell count in that range for the past two years. The third patient had azathioprine therapy initiated to try to improve his intermediate response. After one year, there was no marked improvement, and therapy was discontinued. One patient who had an intermediate response was evaluated for adjunctive therapy and found to have superficial involvement with lymphoma and with a scant dermal infiltrate (Fig. 3A–3C). Adjunctive topical nitrogen mustard ointment therapy was initiated and, after four months, there was clinical improvement in conjunction with histologic improvement (Fig. 3C) in a biopsy from the same site.

Prior to initiation of photopheresis, six of the patients had attempted standard psoralen/ultraviolet A (PUVA) photochemotherapy without success. There were four patients who had PUVA therapy attempted after they had achieved an intermediate response stage. Three were unable to tolerate .5 joules/cm<sup>2</sup> due to an accentuation of erythroderma and malaise. One patient was able to tolerate therapy and has continued on a once-weekly regimen for the past year.

#### *Taper of Therapy*

For those patients with a successful response to therapy, photopheresis treatments were gradually tapered as outlined. In all patients, there was a mild flare of disease activity at some point in the weaning process. This reaction necessitated a return to the four-weekly regimen before once again attempting a taper. One patient has discontinued completely, one is at six-weekly treatments, and four are at five-week treatment intervals.

#### *Tumor Stage Disease*

The preliminary results of treating tumor stage with photopheresis alone showed that tumors did not resolve within a few months of therapy. One patient has a remission of over two years' duration from when total body radiotherapy and photopheresis were begun. A second patient is in the seventh month of remission. Patients treated with spot radiotherapy on photopheresis have had two recurrences each. These were subsequently treated with additional spot therapy.

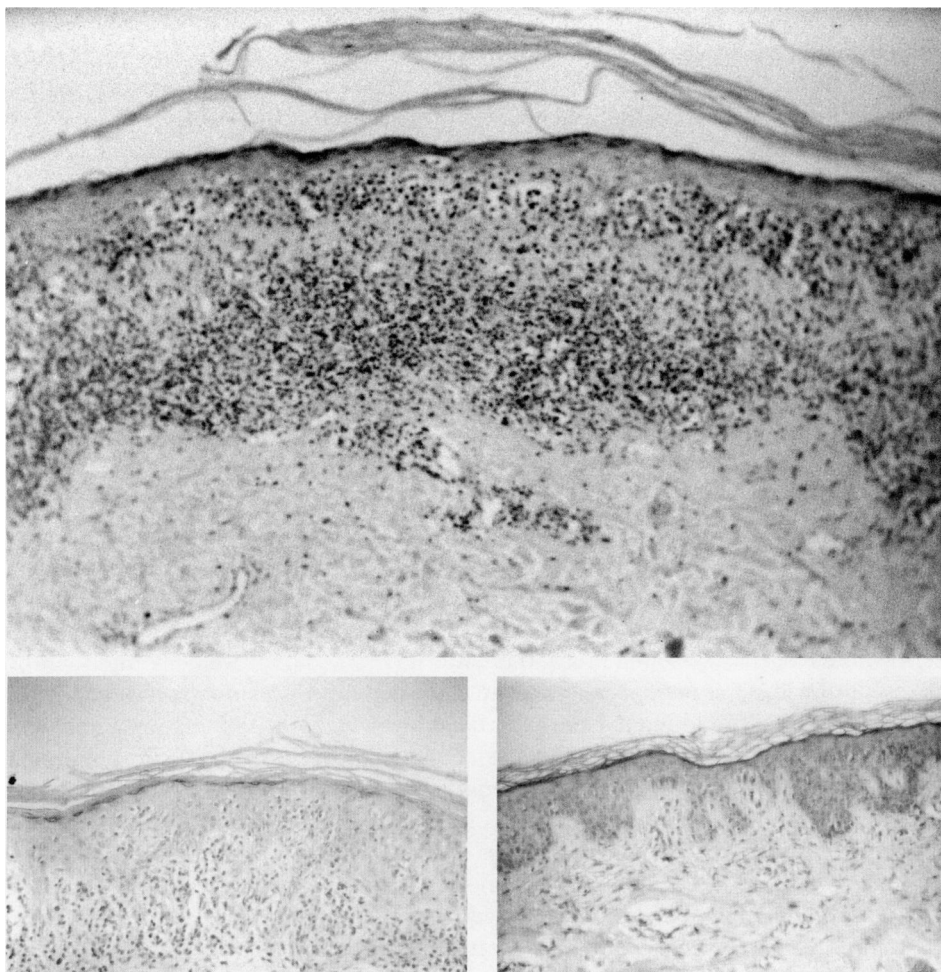


FIG. 3. A skin biopsy showing disease before initiation of photopheresis (A), after 12 months of therapy (B), and after the initiation of nitrogen mustard therapy (C).

### *8-MOP Levels*

The availability of liquid 8-methoxypsoralen in a capsule (OXSORALEN ULTRA®) led to discontinuance of the crystalline preparation. The liquid preparation is more reliably and rapidly absorbed. Therapy was changed to begin with a dose of 0.5 mg/kg oxsoralen Ultra, and blood collection was initiated 60–90 minutes after ingestion. Once the buffy coat collections were completed and the final stage of irradiation had begun, a sample was removed and analyzed for 8-MOP concentration. As can be shown in Fig. 4, there is tremendous variation over a range of mg/kg dosages for 8-MOP. The target “bag level” is to be >50 ng/ml. This goal was reliably achieved in doses >0.5 mg/kg oxsoralen Ultra. If the 8-MOP were extremely elevated (>200 ng/ml) or if the patients were experiencing nausea, the dose was lowered and, on the next treatment, an 8-MOP bag level would be checked.

## BAG LEVELS OF 8-MOP LIQUID PSORALEN

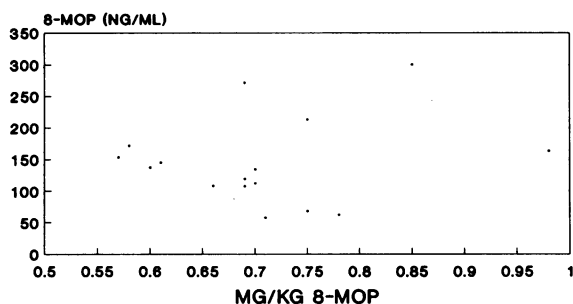


FIG. 4. 8-MOP levels in the treatment bag as a function of dose administered orally.

### *Septic Complications*

Over the two years of operation, there have been approximately 1,400 photopheresis treatments performed at Yale–New Haven Hospital; these include the CTCL patients and those undergoing clinical trials still in progress. To date, there have been no episodes of bacterial sepsis associated with photopheresis. One patient experienced disseminated herpes simplex infection three days after photopheresis. The patient had been pretreated with electron beam followed by six months of chemotherapy. Despite that, he still had erythroderma and tumors at the time of initiation of photopheresis. On his second and third cycles, herpetic infection recurred again at three days after starting photopheresis. The therapy was then discontinued.

### DISCUSSION

The initial study of photopheresis for erythrodermic CTCL demonstrated the ability of this treatment to improve the quality of life for the majority of those treated. The study entry criteria for that report included a white blood count  $<15,000/\text{mm}^3$  [1]. The patients in this report were those with more varied stages of CTCL. Erythroderma patients comprised the majority of the photopheresis treatment population at Yale–New Haven Hospital. The results of therapy in this group are similar to that previously reported in the multi-center trial. Five of 19 patients cleared over 75 percent of their skin involvement, similar to the seven of 29 erythrodermic patients in the original study. In addition, three patients had a minimal response while receiving photopheresis as a first-line therapy. An additional two patients achieved unacceptable responses despite an initial improvement with photopheresis. Taken together, these five patients comprise one-fourth of the Yale–New Haven erythroderma treatment group. Again, this result is similar to the five of 29 erythrodermic patients who did not respond to photopheresis in the earlier report. One difference is that, at 12 months, two of the partial responders had achieved  $>25$  percent clearing, but this condition was not maintained so that, in this report, they would be considered non-responders.

Adjunctive therapy has not been previously reported with photopheresis. In the multi-center trial, patients were limited to 1.0 percent hydrocortisone. With patients in the intermediate response group, there was a need to use adjunctive therapy to yield further improvement. The ideal adjunct would be one which is relatively non-toxic and non-immunosuppressive in order to work with the immunostimulating events of

photopheresis. Low-dose oral methotrexate meets these criteria. In the eight patients who initiated this therapy, five had demonstrable improvement, while three patients stabilized. Even the maximal dose of 15 mg three times a month is so low that concern about liver toxicity does not warrant a liver biopsy so long as patients abstain from alcohol. The synergy of methotrexate with this setting could be multifactorial. Psoralen-thymidine adducts require new thymidine bases in order to be repaired. Interference with repair of photoadducts may represent one mechanism. Another is that cell cycle changes induced by the methotrexate may hold more of the more rapidly growing malignant cells at a more PUVA-susceptible point in the cell cycle. And, finally, given the success of methotrexate in psoriasis, this agent may have an effect against the psoriasiform tissue reaction in general. By itself, low-dose methotrexate has not been reliably effective in treating Sezary syndrome [5,6]. Indeed, many patients in the initial clinical trial and in this report had undergone trials with it before initiating photopheresis.

One of the three patients who were started on azathioprine had a demonstrable improvement with a reduction in white blood count while on azathioprine-photopheresis. This agent is preferentially toxic to T cells and more immunosuppressive than methotrexate. Its use in transplantation is well established. Given the smaller experience with this agent and the more reliable results with the less immunosuppressive methotrexate, it appears azathioprine should be considered as a second-line adjunct.

In one patient, the decision to use topical mustard as an adjunct was made based on the predominance of epidermotropic disease with scant dermal disease. With the improvement noted, it appears these two therapies can be successfully combined.

Given the reactions of erythrodermic patients to PUVA and electron beams, it is questionable that either of these two could be combined in any therapeutic program involving Sezary syndrome patients. The discomfort exhibited by our patients initiating these adjuncts argues against their use in this setting.

The comparison of the five best responding patients to the five least responding patients reveals several interesting guidelines in the selection of patients. As shown in Fig. 1, the fact that the best responders had begun on therapy earlier in the course of their illness suggests that this treatment should indeed be considered the first line of therapy for erythrodermic CTCL. Patients appear to do better when therapy is started earlier in the course of the disease. In addition, those erythroderma patients heavily pre-treated did not respond as well, which may also reflect the fact that they were treated later in the course of their disease. The other finding which appears to correlate with a good response is the presence of suppressor cells in sufficient number. As seen in Fig. 2, the best responders had a smaller CD4 compartment and larger CD8 compartment when compared to non-responders. The latter finding suggests that the CD8 subset may be important for a response to therapy. Whether this subset is stimulated by treatment on the target of therapy is an interesting dilemma. The experimental work by Perez et al. in this issue suggests that suppressor cells are activated by the infusion of photoinactivated lymphocytes.

A gradual taper of photopheresis was found to be the best way to discontinue therapy. In the weaning process, the early recurrence of disease often appeared in the week prior to therapy. This fact suggests that the stimulating effects of photopheresis wear off and that the timing of intervals is important to generating and maintaining a therapeutic response. Based on these results, it is best to wait until the clinical picture



has stabilized for six months after maximum improvement. At that point, intervals are increased by one week per cycle every three treatment cycles.

Adequate 8-MOP levels in the irradiated compartment are important for the photoinactivation of lymphocytes. In the first clinical trial, therapeutic doses of 8-MOP were assessed on the basis of a blood level drawn two hours after an oral dose of crystalline psoralen. The results from our patients suggest that the best way to assess 8-MOP dosage is done on the leukapheresis sample after it has been diluted with saline to facilitate the irradiation process. The target level is  $>50$  ng/ml. This level could be reliably achieved with doses in the range of .5 mg/kg. Also, in light of the "first-pass effect" described by Gasparro et al. in this issue, it is best not to assess 8-MOP absorption the first time a patient has been exposed to the drug. When therapy is initiated, an 8-MOP "treatment bag" level should be checked, provided that the patient has previously ingested psoralen (which many have in the course of attempting PUVA).

In the first published report of photopheresis therapy for CTCL, toxicity was minimal and there was little evidence of immunosuppression. In the group of patients with CTCL reported here, toxicity again appears minimal. Opportunistic infections with atypical mycobacteria and fungi have not appeared. Despite the propensity of erythrodermic patients to develop septic complications due to the loss of cutaneous barrier function, this condition was not a problem. In fact, the prevention of these phenomena by marked cutaneous improvement could probably be demonstrated with a larger number of patients.

The tumor stage/erythroderma patient who experienced three bouts of disseminated herpes after three consecutive cycles of therapy exhibited the most disturbing complication of therapy. Thus, in patients with advanced disease (recurrent tumor stage and erythroderma following radiation and chemotherapy), there may be concern for exacerbating viral disease.

Studies of survival in CTCL have identified several features which worsen the prognosis. The development of erythroderma is associated with a reduction in survival, as is the presence of tumors [7,8]. Given the improvement in erythrodermic patients with photopheresis, it is anticipated that survival statistics will also improve, as this cohort of patients is watched over a long follow-up period. It is also possible that the prolongation of remission in tumor stage patients may also result in prolonged survival in this group as a result of photopheresis.

Photopheresis should not be utilized as a single agent in tumor stage disease. Two patients did not have demonstrable reductions in tumor burden as a result of therapy. Radiotherapy is a useful treatment for ablating tumors. Unfortunately there is a limit as to the total amount of radiotherapy that can be delivered to the skin. Thus, a desirable goal in this stage of the disease is to prolong radiotherapy remissions. The two-year remission in one patient who presented with over 20 tumors is encouraging. From this patient, it is apparent that photopheresis can safely be used as a follow-up to electron beam therapy. The two patients who underwent spot radiotherapy both experienced recurrences elsewhere on their skin. By comparing these results with that of total body radiotherapy, it appears the latter is better for preventing recurrences. Presumably, the total body dosing eradicates microscopic metastases of the disease which are not clinically apparent at the time of spot radiotherapy. The eventual comparison of spot to total body radiotherapy by way of survival statistics will require more patients followed for longer periods of time to be statistically validated.

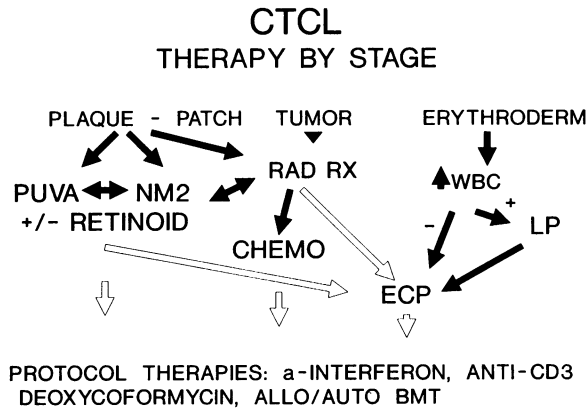


FIG. 5. A treatment algorithm for CTCL shows the role of photopheresis in the management of many stages of the disease. The solid arrows are the currently accepted modalities of therapy. The hollow arrows are those currently under study. ECP, photopheresis; NM2, nitrogen mustard; LP, leukapheresis; BMT, bone marrow transplant.

### SUMMARY

The results of treating erythrodermic CTCL patients with photopheresis are similar to those previously reported. The erythroderma patients did better when therapy was instituted earlier in the course of the disease before the patients were heavily pre-treated. The safety of the procedure has also been demonstrated. Adjunctive therapy has been shown to be synergistic with photopheresis. Thus, this novel photomedical therapy has safely moved from its clinical trial, where its solo effects were noted, to its role as a component of therapy (Fig. 5) of a variety of patients with CTCL.

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