One-Week Treatment With Once-Daily Fluorouracil Cream 0.5% in Participants With Actinic Keratoses

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Actinic keratoses (AKs) are common in fair-skinned individuals with a history of chronic and excessive sun exposure and may progress to squamous cell carcinoma (SCC). Topical fluorouracil is an effective therapeutic option for patients with AKs, but it is associated with substantial skin irritation. The efficacy and tolerability of 1-week treatment using microsponge-based fluorouracil cream 0.5% were analyzed in 356 participants with AK lesions. One-week treatment with once-daily fluorouracil cream 0.5% was significantly more effective than vehicle control in reducing AK lesions and in achieving complete clearance (P<.001). No serious treatment-related adverse events occurred. The most frequent treatment-related adverse events were facial and eye irritations, which were predominantly mild to moderate in severity. No participants in the fluorouracil cream 0.5% treatment group discontinued the study because of treatment-related adverse events. One-week treatment with once-daily fluorouracil cream 0.5% is an effective well-tolerated therapy for AKs. Using this short treatment duration period in combination with cryosurgery may prove beneficial in clinical practice. Extending treatment for up to 4 weeks will further improve AK lesion clearance rates.

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Actinic keratoses (AKs) are neoplastic skin lesions commonly found in sun-exposed areas of skin in individuals with fair complexions.[1,2] The clinical, histologic, and genetic characteristics of AK lesions are similar to in situ squamous cell carcinomas (SCCs).[1,3] It is estimated that the rate of evolution of AK to invasive SCC is approximately 10%,[4] and AK lesions that continue to evolve into SCC may not be visually distinguishable from other AK lesions.[2,5] Thus, treatment of AK lesions is important to avoid progression to SCC.[6,7]

Fluorouracil is the most frequently used topical therapy for AK.[8] Its mechanism of action consists of interference with the synthesis of nucleic acids through its metabolite, 5-fluorodeoxyuridylic acid. This compound inhibits thymidylate synthase, which catalyzes conversion of deoxyuridine 5'-monophosphate to the DNA component thymidine 5'-monophosphate.[9-13] To a lesser extent, incorporation of fluorouracil into RNA also may interfere with RNA synthesis.[9,13-16] Neoplastic keratinocytes in AK lesions have a higher rate of DNA synthesis and repair than keratinocytes in normal skin, suggesting that fluorouracil may preferentially act on AK lesions.[17,18]

The skin irritation caused by some formulations of topical fluorouracil may result in decreased patient compliance and a potentially poor therapeutic outcome.[8] To provide increased efficacy and improved tolerability, a formulation consisting of a 0.5% concentration of fluorouracil was developed

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using a microsponge delivery vehicle. The active ingredient, fluorouracil, is incorporated on the surface of and within porous microspheres.[19] This microsponge-based system has been shown to provide a sustained rate of release of fluorouracil in vitro, thereby potentially maintaining efficacy while reducing local adverse effects.[20] This formulation of fluorouracil is indicated in patients with AKs of the face or anterior scalp as once-daily treatment for up to 4 weeks as tolerated.

We report pooled efficacy and tolerability data from 2 phase 3 studies and 1 phase 4 study involving a total of 356 participants with AK lesions following 1-week treatment with fluorouracil cream 0.5%.

Methods

All of the studies described here were conducted in accordance with the Declaration of Helsinki and were approved by the institutional review board at each participating institution. Written informed consent was obtained from all participants prior to enrollment.

Characteristics of Pooled Studies (2 Phase 3; 1 Phase 4)—Inclusion criteria for the pooled studies included age (18 years or older) and 5 or less visible and/or palpable AK lesions on the frontal scalp (phase 3 only) and/or face (phases 3 and 4). All 3 placebo-controlled, double-blind, parallel-group, multicenter trials examined efficacy and safety in participants receiving a microsponge formulation of fluorouracil cream 0.5% or vehicle control for 4 weeks. Participants were instructed to wash their faces approximately 10 minutes prior to applying treatment, with thorough rinsing and drying with a clean towel. Study medication was applied as a thin film and massaged into the skin each morning or evening at 24-hour intervals. Treatment was applied avoiding the eyes, nose, and mouth, and was to continuously cover the facial area (defined as the superior hairline, the inferior mandibular angle, and the lateral tragus) and frontal scalp (defined as an imaginary longitudinal line drawn directly across the scalp from the right to left tragus), if included as a treatment area.

Primary efficacy variables for this group of studies included reduction from baseline in regional count of visible and palpable AK lesions and complete clearance of AK lesions at the posttreatment follow-up evaluation. Clearance was defined as either a physician global assessment of improvement (PGAI) score of +5, indicating 100% improvement (phase 3), or no AK lesions in the treatment area at posttreatment evaluation (phase 4). Efficacy analyses were based on the intention-to-treat (ITT) populations and included either all participants randomized to treatment (phase 3) or participants with at least 1 postbaseline efficacy measurement (phase 4).

Treatment tolerability was evaluated by monitoring the incidence of adverse events, and data regarding the severity, onset, and duration of adverse events were collected. Participants receiving at least 1 dose of study medication or vehicle control were included in the statistical analyses of tolerability.

The pooled analyses of data for 1-week treatment for the phase 3 and 4 studies are presented here. Complete data from the separate phase 3 studies[21,22] and the phase 4 study[23,24] are reported elsewhere.

Pooled Analysis—Results of the phase 3 and 4 studies were pooled to provide an overall analysis of efficacy of fluorouracil cream 0.5% compared with vehicle control in all study participants. As in the individual studies, efficacy was assessed as the reduction from baseline AK lesion count and the proportion of participants with complete clearance of AK lesions. Percentage reduction in posttreatment AK lesions from baseline was analyzed using an analysis of covariance with treatment, center, and baseline lesions as factors. Between-group differences in complete clearance were analyzed using the Pearson χ^2 test.

Summary statistics were calculated for the incidence of adverse events and the incidence and severity of treatment-related adverse events in the phase 3 and 4 studies. Comparison of the onset of facial irritation between treatment groups was evaluated by the Wilcoxon rank sum test in the pooled phase 3 studies. The incidence and severity of treatment-related adverse events in the phase 3 and 4 studies also were pooled, with descriptive statistics used to provide an overall assessment of the tolerability of fluorouracil cream 0.5% compared with vehicle control.

Results

Participant Demographics and Baseline Characteristics—Overall, a total of 356 participants were enrolled in the phase 3 and 4 studies; 157 participants were randomized to the fluorouracil cream 0.5% groups and 199 were randomized to the vehicle control groups. Four participants discontinued the phase 3 studies, including 3 from the fluorouracil cream 0.5% treatment group because of adverse events (n=2) and voluntary withdrawal (n=1) and 1 from the vehicle control group (voluntary). A total of 7 participants (1 in the fluorouracil cream 0.5% treatment group and 6 in the vehicle control group) discontinued the phase 4 study. One enrolled participant in the phase 4 study was lost to follow-up shortly after the study began. In the pooled phase 3 studies, the ITT and safety populations were identical (n=212).

Table 1.

Participant Demographics and Baseline Characteristics (Intention-to-Treat Population)

	Phase 3 Studies (Pooled Data; 1-Week Treatment)		Phase 4 Study (1-Week Treatment)		Total	
Characteristic	Fluorouracil Cream 0.5% (n=85)	Vehicle Control[a] (n=127)	Fluorouracil Cream 0.5% (n=72)	Vehicle Control (n=70)	Fluorouracil Cream 0.5% (n=157)	Vehicle Control (n=197)
Mean age, y (range)	63.8 (35–86)	64.1 (39–86)	62.6 (33–88)	62.6 (43–84)	63.2 (33–88)	63.6 (39–86)
Sex, n (%)						
Male	70 (82.4)	107 (84.3)	62 (86.1)	57 (81.4)	132 (84.1)	164 (83.2)
Female	15 (17.6)	20 (15.7)	10 (13.9)	13 (18.6)	25 (15.9)	33 (16.8)
Race, n (%)						
White	84 (98.8)	127 (100)	71 (98.6)	67 (95.7)	155 (98.7)	194 (98.5)
Hispanic	1 (1.2)	0 (0)	1 (1.4)	3 (4.3)	2 (1.3)	3 (1.5)
Complexion (Fitzpatrick skin type), n (%)						
Fair/light (I–II)	57 (67.1)	90 (70.9)	48 (66.7)	47 (67.1)	105 (66.9)	137 (69.5)
Medium (III–IV)	27 (31.8)	37 (29.1)	24 (33.3)	23 (32.9)	51 (32.5)	60 (30.5)
Dark (V–VI)	1 (1.2)	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)
Baseline AK lesion count, mean±SD	13.8±7.5	15.9±11.6	22.6±18.2	19.6±13.4	17.8±14.2	17.3±12.3
Eye irritation, n (%)	ND	ND	4 (5.6)	3 (4.3)	4 (5.6)[b]	3 (4.3)[b]
Facial irritation,[c] n (%)	53 (62.4)	81 (63.8)	46 (63.9)	40 (57.1)	99 (63.1)	121 (61.4)
Prior AK therapy, n (%)	52 (61.2)	88 (69.3)	52 (72.2)	39 (55.7)	104 (66.2)	127 (64.5)

Abbreviations: AK, actinic keratosis; SD, standard deviation; ND, not determined.
[a]Participants received vehicle control for 1, 2, or 4 weeks.
[b]In the phase 3 studies, eye irritation was a treatment-related adverse event; therefore, presence and severity of baseline eye irritation were not determined.
[c]Severity of irritation was rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe).

Table 2.

Efficacy of 1-Week Treatment With Once-Daily Fluorouracil Cream 0.5% (Intention-to-Treat Population)

	Phase 3 Studies (Pooled Data)		Phase 4 Study		Total	
Parameter	Fluorouracil Cream 0.5% (n=85)	Vehicle Control[a] (n=127)	Fluorouracil Cream 0.5% (n=72)	Vehicle Control (n=70)	Fluorouracil Cream 0.5% (n=157)	Vehicle Control (n=197)
AK lesions: baseline						
Mean±SD	13.8±7.5	15.9±11.6	22.6±18.2	19.6±13.4	17.8±14.2	17.3±12.3
Median	11.8	12.2	17.0	16.0	14.2	13.6
AK lesions: 1-week treatment						
Mean±SD	5.0±4.6	13.0±12.4	8.2±9.3	13.2±9.4	6.5±7.3	13.1±11.4
Median	4.1	9.8	6.0	11.5	5.0	10.4
Mean reduction in AK lesions from baseline,[b] %	73.9	27.8	61.5	30.3	61.2[c]	24.4
Participants with complete clearance,[d] n (%)	17 (20.0)[c]	2 (1.6)	9 (12.5)[e]	0 (0)	26 (16.6)[c]	2 (1.0)

Abbreviations: AK, actinic keratosis; SD, standard deviation.

[a]Participants received vehicle control for 1, 2, or 4 weeks.

[b]Values in phase 3 studies and total columns are given as least squares mean; values in the phase 4 study column are mean percentage reductions. Percentage reduction in the number of postbaseline lesions is calculated as a percentage of the baseline number (ie, the number of baseline lesions minus the number of lesions at 1 week, divided by the number of baseline lesions multiplied by 100). *P* value derived from analysis of covariance with treatment, center, and baseline lesions as factors.

[c]$P<.001$ vs vehicle control.

[d]For the phase 3 studies, complete clearance is participants with a physician global assessment of improvement score of +5; for the phase 4 study and overall, clearance reflects a final lesion count of zero.

[e]$P=.002$ vs vehicle control.

One participant in the phase 4 study, however, received treatment (vehicle control) but did not have a postbaseline efficacy measurement. As a result, the phase 4 safety population included 1 more participant than the ITT population (n=143 and n=142, respectively).

Demographics and baseline characteristics for the ITT populations for the pooled phase 3 studies, the phase 4 study, and all studies combined are presented in Table 1. Participants in all study groups were comparable in age. Most participants were white males with light complexion. In the pooled phase 3 studies, 61.2% (52/85) of the fluorouracil cream 0.5% treatment group and 69.3% (88/127) of the vehicle control group had received prior therapy for AK lesions, primarily cryotherapy. In the phase 4 study, 72.2% (52/72) of the fluorouracil cream 0.5% treatment group and 55.7% (39/70) of the vehicle control group had received prior therapy for AK lesions. Demographics were similar in the fluorouracil cream 0.5% and vehicle control treatment groups in the pooled phase 3 studies and the phase 4 study, without significant between-group differences.

The number of AK lesions across all treatment groups ranged from 5 to 94 at baseline (data not shown). More than half of the participants in all study groups had facial irritation, including erythema and dryness, with severity ranging from none to severe. Baseline disease characteristics were similar for the fluorouracil cream 0.5% and vehicle control treatment groups in the pooled phase 3 studies and the phase 4 study, without significant between-group differences.

Efficacy—In the pooled phase 3 studies and the phase 4 study, 1-week treatment with fluorouracil cream 0.5% was significantly more effective than vehicle control in reducing AK lesions ($P<.001$)(Table 2). The proportional reductions from the number of baseline AK lesions (derived from least squares mean reduction) were 73.9% for participants treated with fluorouracil cream 0.5% and 27.8% for participants receiving vehicle control ($P<.001$) in the pooled phase 3 studies. In the phase 4 study, the percentage reductions from baseline in the number of AK lesions in all treated areas were 61.5% for participants treated with fluorouracil cream 0.5% and 30.3% for participants receiving vehicle control ($P<.001$). Pooled analysis of the 3 studies at 1 week demonstrated a 61.2% reduction (least squares mean reduction) from baseline in the number of AK lesions in the treatment group compared with 24.4% in the vehicle control group ($P<.001$). Overall, 16.6% (26/157) of participants treated with fluorouracil cream 0.5% experienced complete lesion clearance compared with 1.0% (2/197) of participants in the vehicle control group ($P<.001$). Results from the 2 phase 3 studies demonstrated that 20.0% (17/85) of participants achieved complete clearance of lesions in the fluorouracil cream 0.5% group versus 1.6% (2/127) of participants in the vehicle control group ($P<.001$); phase 4 data demonstrated complete clearance of lesions in 12.5% (9/72) and 0% (0/70) of participants, respectively ($P=.002$). PGAI scores were determined in the 2 pooled phase 3 studies only. One-week treatment with fluorouracil cream 0.5% significantly improved PGAI scores in the active treatment group compared with the vehicle control group (2.66 vs 0.69, respectively; $P<.001$)(data not shown).

Tolerability—The tolerability of 1-week treatment with once-daily fluorouracil cream 0.5% was evaluated by monitoring adverse events in all participants who received at least 1 dose of study medication or vehicle control. Three serious adverse events occurred in the pooled phase 3 studies, none of which were considered to be treatment related by the investigators. In the pooled phase 3 studies, serious adverse events included the death of 1 participant in the fluorouracil cream 0.5% treatment group because of cardiac failure and cardiovascular problems in 2 participants receiving vehicle control. In the phase 4 study, 2 participants in the vehicle control group also had cardiovascular problems. The 4 participants with cardiovascular-related adverse events recovered and completed their treatment. The most frequent treatment-related adverse event in all 3 studies was facial irritation, which was experienced by 56.7% (89/157) of participants receiving fluorouracil cream 0.5% and 42.9% (85/198) of participants receiving vehicle control. In the pooled phase 3 studies, 2 participants from the fluorouracil cream 0.5% treatment group discontinued the study because of adverse events and 1 participant voluntarily withdrew from the study, whereas 1 participant from the vehicle control group voluntarily discontinued study medication but completed follow-up evaluations. In the phase 4 study, 1 participant from the fluorouracil cream 0.5% treatment group and 6 participants from the vehicle control group discontinued the study.

At baseline in the phase 4 study, 63.9% (46/72) and 57.1% (40/70) of participants in the fluorouracil cream 0.5% and vehicle control treatment groups, respectively, experienced facial irritation (Table 3), mostly mild to moderate. Common signs and symptoms of facial irritation included dryness and erythema (data not shown). The incidence of mild, moderate, or severe facial irritation in the pooled

Table 3.

Tolerability of 1-Week Treatment With Once-Daily Fluorouracil Cream 0.5% Based on Incidence of Facial and Eye Irritation Adverse Events (Safety Population)

	Phase 3 Studies (Pooled Data)		Phase 4 Study		Total	
Adverse Event	Fluorouracil Cream 0.5% (n=85)	Vehicle Control[a] (n=127)	Fluorouracil Cream 0.5% (n=72)	Vehicle Control (n=71)	Fluorouracil Cream 0.5% (n=157)	Vehicle Control (n=198)[b]
Facial Irritation[b,c]						
Baseline, n (%)	53 (62.4)	81 (63.8)	46 (63.9)	40 (57.1)[b]	99 (63.1)	121 (61.4)
On study,[d] n (%)	78 (91.8)[e]	83 (65.4)	11 (15.3)	2 (2.8)	89 (56.7)	85 (42.9)
Maximum severity on study, n (%)						
None	7 (8.2)	44 (34.6)	61 (84.7)	69 (97.2)	68 (43.3)	113 (57.1)
Mild	41 (48.2)	72 (56.7)	ND	ND	41 (26.1)	72 (36.4)
Moderate	34 (40.0)	9 (7.1)	ND	ND	34 (21.7)	9 (4.5)
Severe	3 (3.5)	2 (1.6)	11 (15.3)[f]	2 (2.8)	14 (8.9)	4 (2.0)
Eye Irritation[b,e,g]						
Baseline, n (%)	ND	ND	4 (5.6)	3 (4.3)	4 (5.6)[g]	3 (4.3)[g]
On study,[d] n (%)	5 (5.9)	2 (1.6)	9 (12.5)	10 (14.1)	14 (8.9)	12 (6.1)

Abbreviation: ND, not determined.

[a]Participants received vehicle control for 1, 2, or 4 weeks.

[b]In the phase 4 study, baseline irritation data were determined for the intention-to-treat population, whereas on-study irritation data were collected for the all-treated population. In the vehicle control group, these populations consisted of 70 and 71 participants, respectively. As a result, baseline facial irritation percentages are based on a vehicle control group total of 198 participants, while all subsequent percentages are based on a vehicle control group total of 197 participants.

[c]Phase 4 study evaluated severe facial irritation only.

[d]Relation to treatment: possible, probable, or definite.

[e]$P<.001$ vs vehicle control.

[f]$P=.017$ vs vehicle control.

[g]In the phase 3 studies, eye irritation was a treatment-related adverse event; therefore, presence and severity of baseline eye irritation were not determined.

phase 3 studies increased significantly ($P<.001$) in the fluorouracil cream 0.5% treatment group versus the vehicle control group, affecting 91.8% (78/85) and 65.4% (83/127) of participants, respectively (Table 3). Onset and duration of facial irritation were determined in the pooled phase 3 studies only. The median onset was the same (day 4), irrespective of treatment product. In all fluorouracil cream 0.5% treatment groups, the most common signs and symptoms of facial irritation included dryness, erythema, burning, and pain (data not shown). The severity of facial irritation returned to below baseline levels in the phase 3 studies within 1 week of treatment cessation. In the phase 4 study, severe application site reactions were significantly more frequent in the fluorouracil cream 0.5% treatment group (15.3% [11/72]; $P=.017$) than in the vehicle control group (2.8% [2/71])(Table 3) and decreased with time.

Overall, eye irritation was experienced by 8.9% (14/157) of participants receiving fluorouracil cream 0.5% and 6.1% (12/198) of participants receiving vehicle control (pooled phase 3: 5.9% [5/85] vs 1.6% [2/127], respectively; phase 4: 12.5% [9/72] vs 14.1% [10/71], respectively)(Table 3). More than twice as many treatment-related eye irritations occurred in the active treatment group in the phase 4 study than in the pooled phase 3 studies (12.5% vs 5.9%, respectively). At baseline in the phase 4 study, the incidence of eye irritation was similar between the fluorouracil cream 0.5% and vehicle control treatment groups (Table 3), with severity ranging from mild to moderate (data not shown). Both treatment groups demonstrated comparable increases in eye irritation, the severity of which was mostly mild.

Comment

Efficacy—Data from the 2 pooled phase 3 studies and the phase 4 study, with a total of 356 participants with AK lesions, demonstrated that 1-week treatment with once-daily fluorouracil cream 0.5% was significantly more effective than vehicle control in reducing AK lesions from baseline and in achieving AK clearance ($P<.001$). In addition, overall PGAI scores, a secondary efficacy parameter assessed in the 2 pooled phase 3 studies, significantly improved following treatment with fluorouracil cream 0.5% versus vehicle control ($P<.001$). The efficacy of fluorouracil cream 0.5% may be attributed in part to its targeted delivery using the microsponge delivery system. A skin permeation study conducted with human cadaver skin demonstrated that 86% to 92% of the applied dose of fluorouracil cream 0.5% was retained in the skin after 24 hours compared with 54% of fluorouracil cream 5%.[25] Once-daily treatment for 1 week with fluorouracil cream 0.5% resulted in significant lesion clearance rates for the 3 studies compared with vehicle ($P<.001$), but it has been shown that extending treatment for up to 4 weeks resulted in increased lesion clearance rates, ranging from 47.5% to 57.8%.[21-23] More importantly, however, the use of once-daily fluorouracil cream 0.5% for a period of 1 week as part of interval therapy has been shown to increase cryosurgery efficacy. Pretreatment with fluorouracil cream 0.5% prior to cryosurgery has been noted to not only reduce the number of lesions requiring cryosurgery but also to potentially unmask smaller AK lesions that otherwise may not have been clinically evident.[23,24]

Tolerability—In the 2 pooled phase 3 studies and the phase 4 study reported here, the most frequent treatment-related adverse events included facial and eye irritations. The incidence and severity of facial irritation were higher in the fluorouracil cream 0.5% treatment group than in the vehicle control group. Most facial irritation responses were mild to moderate in severity. An increased incidence of eye irritation occurred in the phase 4 study compared with the phase 3 studies, but reactions were mostly mild in severity. The severity of facial irritation returned to below baseline levels quickly in the phase 3 studies (within 1 week of treatment cessation). One serious adverse event was deemed unlikely to be related to fluorouracil cream 0.5% use; all others were considered unrelated to treatment. The incidence and severity of application site reactions, including facial irritation, are consistent with previous reports.[23,24] With time, the occurrence of severe reactions have been reported to decrease with re-treatment.[23] Serious toxicity resulting from topical fluorouracil treatment has been reported only once, in a dihydropyrimidine dehydrogenase–deficient patient who was treated with twice-daily fluorouracil cream 5% for 1 week. Systemic absorption of the fluorouracil cream 5% and the absence of dihydropyrimidine dehydrogenase, which degrades fluorouracil, resulted in severe gastrointestinal tract and hematologic toxicities in this patient.[26] The systemic absorptions of fluorouracil cream 0.5% once daily or fluorouracil cream 5% twice daily applied for up to 28 days by patients with AK lesions were estimated to be 0.55% and 2.4%, respectively.[27] Thus, the systemic exposure associated with topical 1-week treatment with once-daily fluorouracil cream 0.5% is unlikely to pose any systemic safety risks.

Participant Compliance—Participant compliance was determined in the phase 4 study only and was found to be 100% in the fluorouracil cream 0.5% treatment group, which comprised 72 participants. This high compliance rate with 0.5% cream

is notable in light of reports that the irritation response associated with standard topical fluorouracil 5% treatment (twice-daily application for 2–4 weeks) has been reported to result in reduced patient compliance and potentially suboptimal outcomes.[8] The reported finding of 100% participant compliance in this phase 4 study, however, will need to be confirmed in future trials of fluorouracil cream 0.5%.

Conclusion

These 3 studies demonstrated that 1-week treatment with once-daily fluorouracil cream 0.5% provides safe, effective, and well-tolerated therapy for participants with AK lesions. Convenient 1-week treatment with once-daily fluorouracil cream 0.5% may allow for treatment of AK lesions, particularly when used as part of interval therapy in combination with cryosurgery. Extending treatment with fluorouracil cream 0.5% for up to 4 weeks results in increased lesion clearance rates and should be considered as an appropriate continuation of treatment.

REFERENCES

1. Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). *J Am Acad Dermatol*. 2000;42(1, pt 2):11-17.
2. Moy RL. Clinical presentation of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol*. 2000;42 (1, pt 2):8-10.
3. Lober BA, Lober CW. Actinic keratosis is squamous cell carcinoma. *South Med J*. 2000;93:650-655.
4. Glogau RG. The risk of progression to invasive disease. *J Am Acad Dermatol*. 2000;42(1, pt 2):23-24.
5. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol*. 2000;42 (1, pt 2):4-7.
6. Patients urged to seek treatment for actinic keratoses, recommends the American Academy of Dermatology, The American Cancer Society, and the Skin Cancer Foundation. *Cutis*. 1999;63:348.
7. Evans C, Cockerell CJ. Actinic keratosis: time to call a spade a spade [editorial]. *South Med J*. 2000;93:734-736.
8. Dinehart SM. The treatment of actinic keratoses. *J Am Acad Dermatol*. 2000;42(1, pt 2):25-28.
9. Eaglstein WH, Weinstein GD, Frost P. Fluorouracil: mechanism of action in human skin and actinic keratoses. I. effect on DNA synthesis in vivo. *Arch Dermatol*. 1970;101:132-139.
10. Cohen SS, Flaks JG, Barner HD, et al. The mode of action of 5-fluorouracil and its derivatives. *Proc Natl Acad Sci U S A*. 1958;44:1004-1012.
11. Danneberg PB, Montag BJ, Heidelberger C. Studies on fluorinated pyrimidines. IV. effects on nucleic acid metabolism in vivo. *Cancer Res*. 1958;18:329-334.
12. Haggmark A. Studies on resistance against 5-fluorouracil. II. thymidylate synthetase from drug-resistant tumor lines. *Cancer Res*. 1962;22:568-572.
13. Heidelberger C. Fluorinated pyrimidines. *Progr Nucleic Acid Res Biol*. 1965;4:1-50.
14. Parker WB, Cheng YC. Metabolism and mechanism of action of 5-fluorouracil. *Pharmacol Ther*. 1990;48:381-395.
15. Skold O. Enzymic ribosidation and ribotidation of 5-fluorouracil by extracts of the Ehrlich-ascites tumor. *Biochim Biophys Acta*. 1958;29:651.
16. Herrick D, Kufe DW. Lethality associated with incorporation of 5-fluorouracil into preribosomal RNA. *Mol Pharmacol*. 1984;26:135-140.
17. Bataille V, Cunningham D, Mansi J, et al. Inflammation of solar keratoses following systemic 5-fluorouracil. *Br J Dermatol*. 1996;135:478-480.
18. Lawrence N. New and emerging treatments for photoaging. *Dermatol Clin*. 2000;18:99-112.
19. Carac [package insert]. Bridgewater, NJ: Dermik Laboratories; 2006.
20. Jorizzo J. Topical treatment of actinic keratosis with fluorouracil: is irritation associated with efficacy? *J Drugs Dermatol*. 2004;3:21-26.
21. Jorizzo J, Stewart D, Bucko A, et al. Randomized trial evaluating a new 0.5% fluorouracil formulation demonstrates efficacy after 1-, 2-, or 4-week treatment in patients with actinic keratosis. *Cutis*. 2002;70:335-339.
22. Weiss J, Menter A, Hevia O, et al. Effective treatment of actinic keratosis with 0.5% fluorouracil cream for 1, 2, or 4 weeks. *Cutis*. 2002;70(suppl 2):22-29.
23. Jorizzo J, Weiss J, Vamvakias G. One-week treatment with 0.5% fluorouracil cream prior to cryosurgery in patients with actinic keratoses: a double-blind, vehicle-controlled, long-term study. *J Drugs Dermatol*. 2006;5:133-139.
24. Jorizzo J, Weiss J, Furst K, et al. Effect of a 1-week treatment with 0.5% topical fluorouracil on occurrence of actinic keratosis after cryosurgery: a randomized, vehicle-controlled clinical trial. *Arch Dermatol*. 2004;140: 813-816.
25. Levy S, Furst K, Chern W. A comparison of the skin permeation of three topical 0.5% fluorouracil formulations with that of a 5% formulation. *Clin Ther*. 2001;23:901-907.
26. Johnson MR, Hageboutros A, Wang K, et al. Life-threatening toxicity in a dihydropyrimidine dehydrogenase–deficient patient after treatment with topical 5-fluorouracil. *Clin Cancer Res*. 1999;5:2006-2011.
27. Levy S, Furst K, Chern W. A pharmacokinetic evaluation of 0.5% and 5% fluorouracil topical cream in patients with actinic keratosis. *Clin Ther*. 2001;23:908-920.