Chemotherapy of Skin Cancer

Edmund Klein, M.D.
Robert W. Case, B.S.
Gordon H. Burgess, M.D.

Epitheliomas and precancerous lesions of the skin are common tumors of man. Approximately 100,000 new patients with epitheliomas are diagnosed each year and the estimated yearly incidence of precancerous (or actinic) solar keratoses in the United States reaches 5-10 million. Skin cancers are different from other cancers in at least two ways. First, identification can be easily made and biopsy can be readily performed on suspicious lesions. Second, methods for treatment are well known and fairly standard throughout the country; the cure rate approaches 98 percent. Nevertheless, 4,000 individuals in this country die every year of the consequences of skin cancer. Faced with this appalling statistic for a tumor so readily available for diagnosis and therapy, the search continues for different, specialized and more effective methods which can be used in unusual occasions for treatment of cancer and precancers.

Topical 5-Fluorouracil

The topical use of 5-Fluorouracil (5-FU) is a major innovation in the treatment of cancers and precancers of the skin. Because the parameters of skin cancers can usually be identified and because the skin resists absorption, concentrations of medications such as 5-FU can be used on the skin far in excess of what could be tolerated if given intravenously. For example, very large quantities of active chemicals can be applied to an epithelioma without risk to the organism as a whole. Recent studies show that locally administered antitumor agents profoundly affect the course of superficial tumors, eradicating primary cutaneous tumors and palliating cutaneous and subcutaneous metastases of disseminated tumors.

Mode of Action

5-FU has been shown to inhibit DNA synthesis in solid tumors. However, in some precancerous lesions such as actinic keratoses, its exact mode of action is unknown; 5-FU seems to destroy the malignant cell and spare the normal cell. Various theories to account for this phenomenon have been proposed. Studies using the deoxyribose of 5-Fluorouracil (FUDR) on actinic keratoses and basal cell carcinomas suggest that this agent is not more effective than the 5-FU uncombined. The riboside should theoretically be more effective in antitumor activity since it represents the next step in 5-FU metabolism if it is to inhibit tumor cells by competitive inhibition of
thymidylate synthase. The controlling factor may be absorption through cell membrane of the tumor or the barrier membrane of the epidermis. Alternatively, 5-FU (as FUR) may act by preferential incorporation into RNA of tumors, thus producing fraudulent RNA; these may be incompatible with survival of cells or lead to formation of abnormal monomolecules, which may be antigenic. Immunologic reactions may therefore play a role in the cytolytic action of 5-FU. This would explain some of the selectivity on malignant cells as reflected by concurrent healing and tumor destruction. 5-FU or other similar chemical agents may produce changes in the tumor cells that cause certain parts of the cell to act as antigens to the body’s own defense mechanisms. Alternatively, or in addition, the defense mechanisms of the host may only be able to act on the abnormal or malignant tumor cell after it has been damaged by the chemotherapeutic agent.

**Indications**

In general, topical 5-FU represents the present treatment of choice for disseminated actinic keratoses no matter on what area of the body they occur. (Figs. 1, 2 and 3.) It has also been used successfully in the management of multiple superficial basal cell epitheliomas (Figs. 4, 5, 6 and 7) and squamous cell carcinomas in situ when involvement of large areas of the body surface precludes the usual therapy. Topical 5-FU also causes clinically undetectable lesions to undergo inflammatory reactions, making them obvious for treatment and resolution.

**Therapy**

In treating actinic keratoses, the physician must first identify the area of actual or potential involvement—the whole face, the forehead or radiation therapy sites. When the maximum treatment area is delineated, a thin layer of 5-FU preparation is applied, usually twice a day, not only to the visible keratoses but also to the entire intervening area with adequate margins. Because keratoses arising in radiation dermatitis sites seem to be highly sensitive to 5-FU, a small test site should be treated for a few weeks to determine minimal dose levels for treatment of larger areas and to avoid excessive reactions.

The patient must be cautioned that he will probably see no change in his skin during the first week or two of treatment. But, gradually, he will observe a predictable series of epidermal changes, beginning with the formation of erythema in the lesions, followed usually, but not necessarily, by crusting, ulceration and eventual healing. These changes usually take place over a period of two to three weeks, depending on the severity of the

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**Fig. 2.** After two weeks’ treatment with 5 percent FU cream.

**Fig. 3.** Six months post-therapy.
reaction and the size of the lesion. The patient must also be advised to continue using the preparation even though his face may become noticeably red. The therapist should make sure that the procedure is carried out at a time when the patient is available for a two to three month period for therapy prior to instituting the topical preparation. Since this type of therapy is usually elective, it can be delayed to a time convenient for both the physician and the patient. Patients are usually able to tolerate keratoses which may get bright red and in some cases ulcerate and bleed and need only minimal analgesia. Healing, which may take as long as one or two months following therapy proceeds with the formation of granulation tissue and re-epithelialization, with eventual appearance of normal skin.

Some patients with a high propensity to develop actinic keratoses may need retreatment at intervals of approximately two years. However, most patients remain free of keratoses for periods of many years. There is no contraindication to the repeated use of 5-FU in actinic keratoses and tolerance to this drug has been found even after repeated applications.

Side Effects

Systemic toxicity has not been encountered even when large areas of the body surface (up to 50 percent) were treated for six months with five percent 5-FU cream. Although 5-FU is absorbed to a limited extent through the skin, we have been unable to detect it by isotope labeled tracer studies in serum, urine, feces and exhaled carbon dioxide. Local side effects, such as irritation, pain with pruritus and burning, occur most frequently in nasolabial folds and in wrinkles. Avoid using topical 5-FU in these areas unless absolutely necessary.

Allergic reactions have been encountered in less than 0.1 percent of patients and are caused in many cases by chemicals present in the vehicle rather than by the 5-FU itself. If the patient shows some acute allergy or intolerance to the preparation, evidenced by the vesiculation and erythema of all normal skin between the lesions, termination of therapy is necessary. Alternate vehicles and patch testing are mandatory before a second course of 5-FU is undertaken.

Exposure to sunlight should be avoided since even mild erythema from sunburn may have a strong potentiating effect on the reaction to treatment with 5-FU. Acute inflammatory reactions of the skin should be managed in the usual way with the application of cold compresses and topical corticosteroids; on occasion, a brief course of systemic corticosteroids may be indicated.

When the topical application of 5-FU
is continued beyond the maximal erythematous reaction, the keratoses sites begin to heal although 5-FU cream is still applied. This is adequate evidence that 5-FU does not interfere significantly with the functions of normal epidermal cells, which grow to heal the defect while the malignant cells are being eradicated. Cosmetic results of 5-FU therapy are therefore eminently satisfactory and scarring is almost never seen.

Results
An 80 percent cure rate has been achieved in over 1,000 cases of superficial basal cell epitheliomas treated with 5-FU twice daily for approximately four weeks. The response rate in nodular infiltrated lesions has been satisfactory. In selected cases in which epitheliomas cannot be adequately treated by surgery or radiation therapy, 5-FU applied over a number of weeks or even months has shown excellent results in controlling or even eradicating previously unmanageable tumors of the skin.2

Topical application of 5-FU has caused partial to complete regression in tumors metastatic to the skin. Palliation of lymphomas, sarcomas, melanomas and some other tumors has been achieved by treating cutaneous lesions with topical 5-FU or other similar agents.

The topical chemotherapy of skin cancer has provided a model system for the investigation of relationships between host, tumor and therapeutic agents, permitting the exploration of basic aspects of tumor biology and resulting in the development of immunotherapeutic procedures for cancer.

Despite the notable success of 5-FU as a topical chemotherapeutic agent, the search continues for even more efficacious agents which can be used for nodular epitheliomas and other solid tumors. Preliminary studies applying 6-deazadenosine to nodular basal cell epitheliomas of the skin have shown cure rates approaching 100 percent. It seems likely that in the reasonably near future additional compounds will be proven effective against skin cancers and extended to other types of cancer, as well.

References
1. Schwartz, S. H.; Bardos, T. J.; Burgess, G. H., and Klein, E.: Cytostatic and immunologic activity of 5-MUDR in the management of multiple superficial basal cell epitheliomas. J. Med. 1: 174-179, 1970.
2. Litwin, M. S.; Ryan, R. F.; Reed, R. J., and Krementz, E. T.: Topical chemotherapy of advanced cutaneous malignancy with 5-Fluorouracil creme. J. Surg. Oncology 3: 351-365, 1971.