MEDICAL INTELLIGENCE

PREVENTION OF DOXORUBICIN-INDUCED HAIR LOSS WITH SCALP HYPOTHERMIA

JUDITH C. DEAN, R.N., M.S.,
SYDNEY E. SALMON, M.D.,
AND KATHERINE S. GRIFFITH, R.N.

THE psychological impact of chemotherapy-induced alopecia represents one of the more devastating side effects of cancer chemotherapy and, in some instances, leads patients to refuse potentially curative chemotherapy. The problem of alopecia is severe when patients are treated with the anthracycline antibiotic, doxorubicin (adriamycin), which is beneficial in many types of cancer (e.g., breast, lung, ovary, sarcomas, lymphomas, and leukemias).[1-6] In 1973, Luce and his co-workers achieved good protection against doxorubicin-induced alopecia in 12 of 15 patients by means of regional direction of chilled air to the scalp.[7] More recently, Edelstyn's group used cryogel packs held on the scalp with stockingette and observed good protection against hair loss over a short time in 20 of 40 patients who received 50 mg of doxorubicin in combination chemotherapy.[8]

From the theoretical standpoint, two advantages could accrue from scalp hypothermia: vasoconstriction resulting from scalp hypothermia would decrease the amount of drug reaching hair follicles, and cellular uptake of the drug would be reduced (like many other drugs, doxorubicin requires temperature-dependent metabolic processes for cellular uptake).[9] We decided to follow up on the promising leads of Luce and Edelstyn by systematically testing a simple and readily available technique for induction of scalp hypothermia in our patients with cancer who receive a well defined doxorubicin-cyclophosphamide combination-chemotherapy regimen that routinely causes severe or total alopecia.[1-6] We sought to determine whether long-term protection against doxorubicin-induced hair loss could be achieved with repeated hypothermic treatment. To obtain information on time–dose relations of scalp hypothermia and drug injection, we assessed the relation between doxorubicin dosage and hypothermic protection against alopecia and also measured the rate and profundity of the change in scalp temperature achieved with hypothermia.

Cancer patients receiving doxorubicin-cyclophosphamide combination chemotherapy were treated prophylactically over many months with a brief scalp-hypothermia procedure at the time of each doxorubicin injection. The hypothermia procedure, which uses crushed ice in disposable plastic bags, is simple, inexpensive, well tolerated, and universally available. It has proved to be quite effective in preventing alopecia, and most patients studied had good or excellent preservation of scalp hair, usually obviating the need for wigs for cosmetic purposes. An even higher proportion of patients receiving doxorubicin in doses of 50 mg or less had good protection. Thus, the protective effect of scalp hypothermia was inversely related to doxorubicin dosage, and a longer duration or more profound hypothermia might prevent alopecia when doses are greater than 50 mg.

METHODS

All 33 patients were beginning doxorubicin-cyclophosphamide chemotherapy. The median age was 53 years, and all patients except one were female. Tumor types were breast (29 patients), ovarian (two patients), uterine (one patient), and prostatic (one patient). Patients who were bald, those with leukemia or scalp metastases, or those who previously had cranial irradiation, vasculitis, or cryoglobulinemia were ineligible. For our standard surgical adjuvant-therapy breast-cancer protocol Stage II and III patients received doxorubicin, 30 mg per square meter of body-surface area intravenously, on Day 1 and cyclophosphamide, 150 mg per square meter by mouth, on Days 3 to 6 every three weeks for eight treatment cycles.[4] In our earlier experience, over 95 per cent of 120 women entered on this protocol had total alopecia during the course of treatment.[4] Patients with advanced breast, ovarian, uterine, and prostatic cancer received 25 per cent higher doses of these same agents.[4,5] To simplify doxorubicin preparation and administration, dosages were routinely rounded to the nearest 10 mg.

The hypothermic treatment was carried out as follows: foam pads cut from the heels of disposable hospital slippers were first placed over the ears to insulate them against excessive exposure to cold. Ice packs consisting of crushed ice in two 61 by 61-cm plastic bags were then applied (one in front and one in back) to cover the entire scalp. The ice packs were secured with 15-cm-wide Ace bandages wrapped in turban style. The "ice turban" was applied five minutes before each doxorubicin injection and left in place until 30 minutes after the injection, for a total of 35 to 40 minutes of scalp hypothermia.

Scalp hair was evaluated by both the patient and the examining nurse before the initiation of chemotherapy and after the completion of each cycle of treatment. In addition to clinical assessments, routine serial photographs of the scalp were obtained. Written, informed consent was obtained for the serial hypothermic treatments and the photographic documentation. The graded rating scale of protection from hair loss was excellent (0 to 25 per cent loss); good (25 to 50 per cent loss); moderate (50 to 75 per cent loss); or poor (75 to 100 per cent loss). Patients with at least good protection do not usually require wigs for cosmetic purposes. Results of serial ratings on the patients studied were summarized statistically with the "life-table" method of Kaplan and Meier[10] and were also related to the dosage of doxorubicin.

Measurements of the rate and extent of scalp cooling with the standard icing procedure were determined on two of us (J. D. and K. G.) with use of a continuously recording multichannel electronic thermometry system,[11] five subcutaneously placed thermometer probes, and a "systemic" esophageal or rectal thermometer. A thermographic camera was used to monitor temperatures below the hairline.

From the Section of Hematology and Oncology and the Cancer Center, University of Arizona College of Medicine, and the Tucson Veterans Administration Medical Center (address reprint requests to Judith Dean at the Tucson Veterans Administration Medical Center, South 6th Ave., Tucson, AZ 85723).

Supported in part by research grants (CA-17094, CA-23074, and CA-14612) from the National Institutes of Health.

Results

The scalp-icing procedure reduced doxorubicin-induced alopecia substantially in relation to our extensive previous experience with this drug combination. Good protection against hair loss was frequently maintained for the full six to eight-month period of doxorubicin administration (Fig. 1). Overall, 20 of the 33 patients studied had good protection against hair loss throughout all cycles of treatment and did not usually require wigs or have psychologic sequelae related to alopecia. At least good protection against alopecia was observed in almost all patients after the first cycle of treatment and in 70 per cent thereafter. Excellent preservation was observed in most of the patients through the first course of treatment but diminished rapidly thereafter (Fig. 1).

The degree of protection due to hypothermia was clearly related to the doxorubicin dose administered (Fig. 2). All patients who received 40-mg doses maintained good or excellent protection, and all but one of those receiving 50-mg doses had at least good protection. Fewer patients receiving 60 to 80-mg doses had good protection. Only one patient receiving 70 to 80-mg doses retained more than 50 per cent of her hair.

Hypothermia was well tolerated when carried out repeatedly over six to eight months of treatment. Side effects included a "cold feeling" during treatment and transitory mild dizziness at the end of the ice application. Some patients wore sweaters or blankets but most were comfortable with a towel around their necks. Patients with some alopecia had increased local cold sensation as the amount of hair present decreased.

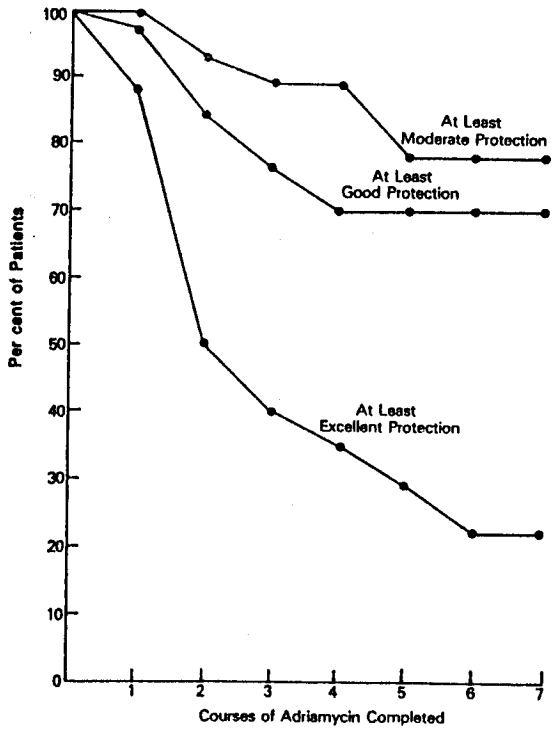

Figure 1. "Life-Table" Plot of Preservation of Scalp Hair. Although the proportion of patients with excellent protection fell over the entire treatment period, those with at least good protection reached a stable plateau.

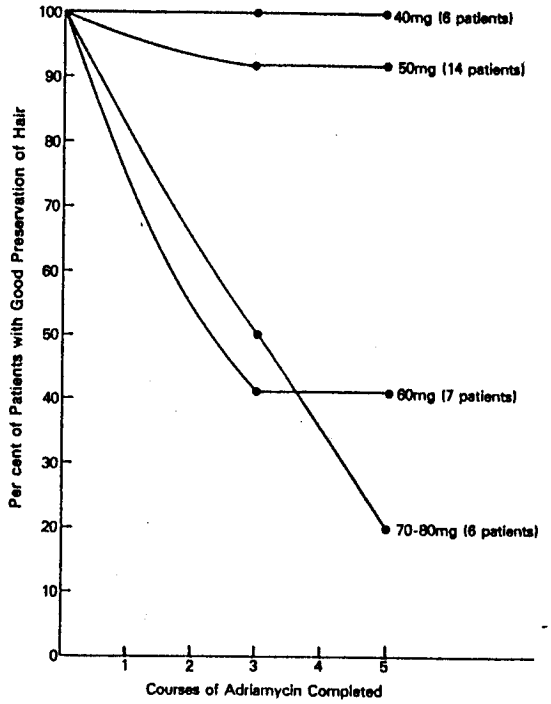

Figure 2. "Life-Table" Plot Relating the Preservation of Scalp Hair to the Dosage of Doxorubicin (Adriamycin) Injected. Scalp hypothermia as administered with our protocol gave good protection when doses were 50 mg or lower.

Serial measurements of scalp temperature in two female subjects undergoing scalp hypothermia yielded identical results. Scalp temperature fell from 37 to 32°C within five minutes of icing and to 26°C within five more minutes, and then stabilized at 23 to 24°C thereafter. Systemic temperature fell less than 0.5°C. Thermography showed constricted venous-drainage channels on the forehead below the ice turban. Scalp temperature returned to the systemic level within 10 minutes after cessation of hypothermia.

Discussion

This simple approach to prevention of doxorubicin-induced alopecia was predicated on promising early reports[7,8] and a straightforward scientific rationale. Although doxorubicin is known to have a relatively long terminal half-life, the peak plasma concentration during the initial distribution phase is transient and followed by a rapid fall in the plasma concentration over the first 30 minutes.[12] Thus, a relatively brief period of scalp hypothermia would be expected to protect against the peak local cytotoxic concentration. However, when summarizing our empirical trial we questioned whether the time-dose relations of hypothermia and doxorubicin were optimal, and we therefore measured scalp temperatures. Inasmuch as it takes 10 minutes for scalp temperature to reach a minimum, we now believe that scalp icing

should be lengthened to 10 minutes before the drug is injected. We are also studying a longer total duration of hypothermia in patients receiving more than 50 mg of doxorubicin. Colder temperatures may also be worth investigating. However, since the 50-mg dose has been most commonly used for patients in our standard breast-cancer adjuvant-treatment program, current data permit the conclusion that the hypothermia technique described is effective at reducing doxorubicin-induced alopecia at this dosage. From the practical standpoint, Edelstyn reported difficulty in maintaining cryogel packs in good apposition with the scalp.[8] In contrast, the more malleable packs of crushed ice that we used could be readily held in place with an elastic bandage.

Inasmuch as our patients received cyclophosphamide by mouth several days after hypothermia, icing had no effect on alopecia induced by this agent.[13] We believe that scalp hypothermia can be used routinely with doxorubicin for the tumor types that we treated, for thyroid, gastric, and pancreatic cancer, and for adjuvant therapy of various tumors (e.g., osteosarcoma). However, we caution that it not be used in leukemias or other neoplastic diseases in which numerous tumor stem cells may be present in the scalp. Additional studies of scalp hypothermia and other intravenously administered drugs that induce alopecia are needed.

We are indebted to Thomas Moon, Ph.D., for biostatistical assistance, to H.-S. G. Chen, Ph.D., for providing data on pharmacokinetic modeling, to Thomas Cetas, Ph.D., for carrying out the thermometry measurements, to Terence Herman, M.D., and Patricia Inscore for useful suggestions, and to Patricia Stanley, R.N., Aurelia Chester, R.N., and the staff of the Cancer Center for their cooperation.

References

1. Wasserman TH, Comis RL, Goldsmith M, et al: Tabular analysis of the clinical chemotherapy of solid tumors. Cancer Chemother Rep 6:399-419, 1975
2. Blum RH, Carter SK: Adriamycin: a new anticancer drug with significant clinical activity. Ann Intern Med 80:249-259, 1974
3. Dreizen S, Bodey GP, Rodriquez V, et al: Cutaneous complications of cancer chemotherapy. Postgrad Med 58(6):150-158, 1975
4. Jones SE, Durie BGM, Salmon SE: Combination chemotherapy with adriamycin and cyclophosphamide for advanced breast cancer. Cancer 36:90-97, 1975
5. Lloyd RE, Jones SE, Salmon SE, et al: Combination chemotherapy with adriamycin (NSC-123127) and cyclophosphamide (NSC-26271) for solid tumors: a phase II trial. Cancer Treat Rep 60:77-83, 1976
6. Wendt A, Jones SE, Salmon SE, et al: Adjuvant treatment of breast cancer with adriamycin-cyclophosphamide with or without radiation therapy. Adjuvant Therapy of Cancer II. Edited by SE Jones, SE Salmon. New York, Grune & Stratton, 1979, pp 285-293
7. Luce JK, Raffetto TJ, Crisp M, et al: Prevention of alopecia by scalp cooling of patients receiving adriamycin. Cancer Chemother Rep 57:108, 1973
8. Edelstyn GA, MacDonald M, MacRae KD: Doxorubicin-induced hair loss and possible modification by scalp cooling. Lancet 2:253-254, 1977
9. Hill BT, Price LA, Goldie JH: The value of adriamycin in overcoming resistance to methotrexate in tissue culture. Eur J Cancer 12:541-549, 1976
10. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
11. Cetas TC, Connor WG: Thermometry considerations in localized hyperthermia. Med Phys 5:79-91, 1978
12. Chen H-SG, Gross JF: Physiologically based pharmacokinetic models for anticancer drugs. Cancer Chemother Pharmacol 2:85-94, 1979
13. Single Agents in Cancer Chemotherapy. Edited by RB Livingston, SK Carter. New York, Plenum Publishing Corporation, 1970, pp 25-80

CURRENT CONCEPTS IN CANCER

Hypoxic Sensitizers — Implications for Radiation Therapy

J. Donald Chapman, M.Sc., Ph.D.

THE proliferative capacity of human cells can be destroyed by ionizing radiation, and the rate of killing by radiation is 2.5 to three times higher in the presence of oxygen than under hypoxic conditions. Since solid tumors often have zones of necrosis and consequently are likely to contain hypoxic yet viable cells, this radiobiologic effect may have implications for cancer therapy. Radioresistant tumor cells that survive treatment can become reoxygenated and lead to a recurrence of the disease.

A recent analysis of 2803 patients with carcinoma of the cervix treated with radiation therapy indicated that those with hemoglobin levels of 12 g per 100 ml or less had a higher rate of recurrence of pelvic cancer and also a lower rate of cure than did those with hemoglobin levels greater than 12 g per 100 ml.[1] Blood transfusions to anemic patients to maintain hemoglobin levels over 13.5 g per 100 ml improved the survival of patients with Stage II B and III disease. Additional procedures designed to increase the radiosensitivity of hypoxic cells within tumors include the use of hyperbaric oxygen chambers, the use of high linear-energy-transfer radiations for which the effect of oxygen is less pronounced, and the use of drugs that mimic the sensitizing effect of oxygen. The approach involving drugs has been developed over the past 10 years and shows promise of improving current clinical practice by means of the direct radiosensitization of resistant tumor cells.

Drugs selected to improve radiotherapy by sensitizing tumor cells are also selectively toxic to hypoxic cells and bind selectively to these cells as a result of metabolism or radiation. These additional features of hypoxic sensitizers may be of clinical value in cancer chemotherapy and diagnosis.

Direct Radiosensitization of Hypoxic Cells

Early studies were performed with various chemicals to determine if radiosensitizing activity could be correlated with a specific chemical property. Adams and Cooke[2] suggested that electron affinity, which had previously been mentioned in a mechanism proposed to explain the radiosensitizing effect of molecular oxygen, was the dominant property that conferred radiosensitizing potential on chemicals.[3] Chapman et al.[4] showed that a threshold in electron affinity near to that of nitrobenzene (half-wave reduc-

From the Department of Radiation Oncology, Cross Cancer Institute, Department of Radiology, University of Alberta (address reprint requests to Dr. Chapman at Radiobiology, Cross Cancer Institute, 11560 University Ave., Edmonton, Alberta, Canada T6G 1Z2).