Preventing hair loss during adriamycin therapy

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ABSTRACT Adriamycin, a relatively new antineoplastic antibiotic, is currently undergoing extensive clinical trials because of its significant antitumor activity. A distressing side effect of the drug, however, is the marked hair loss or alopecia which occurs when cumulative doses of 180–315 mg/m^2 of body surface area are received. This study attempted to prevent this usual hair loss by inducing scalp ischemia just prior to, during, and for 15 minutes after adriamycin injections by means of a special sphygmomanometer cuff inflated to 50 mm Hg above systolic blood pressure.

Study subjects were randomized into control or experimental groups. Patients in the experimental group received the cuff treatment with each injection of adriamycin until 180–315 mg/m^2 was received. Hair loss was measured by independent judges' ratings of pre- and poststudy photographs. The cuff procedure significantly reduced the amount of hair loss experienced by patients in the experimental group. Approximately 3 weeks after critical dosages were received, patients in the experimental group had experienced a 17 ± 14% loss of hair while patients in the control group experienced a 69 ± 32% loss.

Introduction

Adriamycin is an anthracycline antibiotic discovered in 1967 which has shown significant clinical activity against most histological cancer types.[7] It has induced regressions in adult and childhood solid tumors as well as hematologic malignancies.[3]

Adriamycin's potency seems to be based on the fact that it is not cell cycle specific.[16] Rather, it penetrates cells and either adlineates to or intercalates between cellular chromosomes, thereby interrupting or slowing cellular progression.[20,27] The drug cannot cross the blood–brain barrier and is therefore ineffective against primary or metastatic cancers of the brain.[10]

Like most antineoplastic agents, adriamycin has certain toxic side effects. These side effects are dose-related, predictable, and reversible.[3] Dose-limiting side effects include leukopenia, anemia, thrombocytopenia, and cardiomyopathy.[3] Toxicities of a milder nature include transient nausea, vomiting, and anorexia.[3] One particularly distressing side effect of the drug is the almost total hair loss experienced by patients who receive cumulative doses of 180–315 mg/m^2 of body surface area.[4,11,28]

Although hair regrowth does occur, clinical interviews indicate that the onset of alopecia is psychologically traumatic.[5] Sudden hair loss has been noted to have profound psychologic effects on children, especially adolescents; the emotional distress associated with alopecia is only partially eased by the use of wigs.[24]

Literature Review

Because of the potentially debilitating psychological effects of chemotherapy-induced alopecia, several antiepilating procedures have been investigated. Investigators have tried to prevent hair loss from occurring by: 1) placing an icepack on the patient's head, 2) tightly tying a piece of tubing about the patient's head, or 3) encircling the patient's head with a special scalp sphygmomanometer and inflating the cuff to various pressures, just prior to, during, and after injection of epilating drugs.[14,17,23,24,29] The purpose of each of these procedures is the reduction or occlusion of blood flow to hair follicle cells until original plasma concentrations of epilating drugs are absorbed or eliminated by other cells. With the exception of the icepack, investigators reported re-

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TABLE I

Plasma Half-Lives of Drugs Causing Hair Loss Reported in the Literature

Drug	Plasma Half-Life Time (Hours)	Authors
Adriamycin	1.10	Benjamin et al.[2]
Methotrexate	0.75	Dedrick et al.[8]
5-Fluorouracil	1.00	Ahmann, et al.[1]
Cytoxan	Rapid	Mihich[21]
Vincristine	Extremely short	Mandel[19]

ducing the amount of hair loss usually experienced by patients receiving epilating chemotherapy.[14,17,23,24] Although these investigations were not conducted among patients receiving adriamycin, Arnold Lyons reportedly prevented hair loss among patients receiving drugs with plasma kinetics similar to those of adriamycin, namely, 5-fluorouracil and methotrexate.[17] (See Table I.) To do so, Lyons inflated a special scalp tourniquet placed around the patient's head to 240 or 300 mm Hg prior to, during, and "for at least seven minutes" after injections of cytoxan, methotrexate, vincristine, and 5-fluorouracil.[17]

Although Lyons' pneumatic tourniquet procedure and the tubing tournique procedure were reported as effective methods of preventing hair loss caused by certain antineoplastic drugs, other considerations rule out replication of either study. The induction of ischemia with a tubing tourniquet is not recommended for two reasons: 1) inability to control the pressure exerted on underlying tissues, and 2) the high probability of causing compression damage to underlying nerves.[6,12,22,25,26] The pneumatic tourniquet has been recommended because: 1) the amount of pressure applied to a body surface can be controlled, 2) the pneumatic tube distributes uniform pressures over unequally yielding tissues, and 3) there is less probability of compression damage to nerves.[6,12,15,25]

Concern for the protection of underlying tissues is such that some physicians recommend pneumatic cuff pressures be set at pressures not "to exceed preoperative systolic pressure by much more than 70 mm Hg."[26] Rationale for these recommended cuff pressures is based on Hinman's study of operative systolic blood pressure rises. Hinman noted usual systolic blood pressure rises to be 40 mm Hg "with some increases as high as 70 mm Hg during respiratory distress."[15] The duration of ischemia recommended by physicians is obscure.[6,25]

Though few physiological studies of the effects of tourniquet-induced ischemia on underlying human tissues exist, certain studies seem to establish relatively safe time–pressure parameters. Denny-Brown and Brenner demonstrated that direct pressure of 150 mm Hg to nerves will cause nerve conduction to cease in 1 hour.[9] Although the relationship of external to internal pressure is unknown, Lundborg reported that an external inflation pressure of 700 mm Hg was required to produce mean internal pressures of 141 mm Hg on the intact sciatic nerves of rabbits.[18] Comparing tissue metabolites from ischemic and nonischemic extremities during tourniquet-controlled knee-joint and low leg fracture operations, Haljamae and Enger found that metabolic changes in ischemic muscle tissue were reversible up to 1½ hours.[13] Because of the proximity of cranial nerves to the body surface, these investigations suggest that ischemia induced at pressures of not much more than 150 mm Hg for less than 1 hour may be physiologically safe.

Purpose of the Study

The purpose of this study was to determine whether a special pneumatic scalp tourniquet inflated to 50 mm Hg above systolic blood pressure prior to, during, and for 15 minutes after injection of adriamycin chemotherapies would reduce the amount of hair loss usually experienced by patients receiving cumulative doses of 180–315 mg/m^2 of body surface area.

Methodology

The study was conducted from April to October 1976, in the Oncology Department of a large Southern teaching hospital. Drug protocols in effect during this period were those of the Southeastern Cancer Chemotherapy Study Group.

Subjects

All patients expected to receive a course of adriamycin chemotherapy from the hospital's Oncology Service were eligible for inclusion if they met the following criteria:

1. Not bald.
2. No diseases known to cause hair loss.
3. No observable epilating effects from previous chemotherapy.
4. Not hypertensive.
5. No brain metastasis.
6. Not leukemic.
7. No significant arteriosclerotic disease.
8. Interested in entering the study.
9. Referred by their doctors to the study investigator.

Following referral, the investigator verbally explained the purpose and design of the study and offered to demonstrate the tourniquet procedure to the patient. Each patient was also given the same information in

TABLE II

Patient Intake and Exclusion

Patient Intake and Exclusion		No. of Subjects
Total Started on Adriamycin		24
Excluded by Study Entry Criteria		6
Brain metastasis	1	
Hypertension	1	
Atrial fibrillation	1	
Lack of sufficient scalp hair	2	
Transfer from facility	1	
Referred, but missed		4
Refused		1
Consented		13
Failure to Receive Total Adriamycin Dosages of 180–315 mg/m^2		6
Failure to keep return appointment	1	
Chemotherapy changed	3	
Treatment incomplete	1	
Deceased	1	
Chose to Discontinue Tourniquet Treatment		1
Study Patients with Complete Data		6

written form. Patients were assured verbally and in writing that their decision to enter or not enter the study would have no bearing on their chemotherapy treatments and that they could withdraw from the study at any time. Following this explanation, patients who were interested in entering the study were asked to sign a written consent form.

During the time alloted to the study, 24 patients were started on adriamycin chemotherapy protocols. Of these, 13 were accepted into the study. Table II shows subject inclusion and exclusion. Of the 13, six patients (three in the experimental group and three in the control group) received 180–315 mg/m^2 of adriamycin and had complete study data.

Method

After consenting to enter the study, patients were randomized into either a control or experimental group and a prestudy photograph of scalp hair was taken. Patients in the experimental group had the scalp tourniquet applied and inflated to 50 mm Hg above systolic blood pressure prior to, during, and for 15 minutes after each injection of adriamycin chemotherapy. (Adriamycin chemotherapy was usually given once every 3 weeks.) This procedure was repeated until cumulative doses of 180–315 mg/m^2 were received. The same calibrated sphygmomanometer was used throughout the study. Patients in the control group did not have the tourniquet applied. Approximately 3 weeks after each patient had received cumulative doses of 180–315 mg/m^2 of adriamycin, a poststudy photograph of scalp hair was taken.

Determination of hair loss

The amount of hair lost by patients in the study was rated by three graduate students specializing in Oncological Nursing. Evaluations by the judges took place independently of each other. To maintain objectivity, patient group assignment was not identified. To insure that each judge received identical instructions, a written set of instructions describing the rating procedure was used. Before rating study subjects, each judge was first asked to practice rating a series of six pictures representing individuals with varying degrees of hair loss using scales and rating forms developed for the study. Percentages of hair loss was accessed on scales marked in 5% intervals. Each practice photograph was rated independently of each other and on separate scales. On completing the practice session, each judge was given sets of pre- and poststudy photographs to rate. The sets of study photographs were rated independently of each other. Each judge repeated the entire rating procedure 3–4 days later. Ratings of the amount of hair lost by patients in the study were tested for intra- and interjudge reliability with Pearson's Product-Moment Correlation Coefficient and were found to be consistent and reliable (p = 0.0001–0.0002).

TABLE III

Characteristics of Patients Receiving 180–315 mg/m^2 of Adriamycin by Treatment and Control Group

Patient	Average Dose of Adriamycin (mg/m^2)	Number of Doses of Adriamycin	Total Dose of Adriamycin (mg/m^2)	Percent Hair Loss[a]	Weeks in Study
Treatment Group					
1	100	2	200	25	6
12	60	3	180	1	9
13	60	4	240	26	14
Control Group					
2	63	3	190	80	9
3	100	2	220	95	5
6	100	3	300	33	10

[a] Approximately 3 weeks after receiving specified doses.

TABLE IV

Number of Patients Experiencing Greater or Less than 30% Hair Loss by Experimental and Control Group

	Control Group (No Tourniquet)	Treatment Group (Tourniquet)
<30% Hair loss	0	3
>30% Hair loss	3	0

Results

The mean hair loss percentage for each patient was calculated by averaging ratings of the three independent judges (see Table III). Ratings were then categorized according to whether hair loss was greater or less than 30%. (This percentage marks the point at which patients perceive themselves as becoming bald.) These data are displayed in Table IV. Using Fisher's Exact Probability Test, the difference in the proportion of individuals in the experimental and control group experiencing a greater or less than 30% hair loss was found to be statistically significant. ($p = 0.05$). Three weeks after receiving cumulative doses of 180–315 mg/m^2 of adriamycin, patients in the experimental group had lost only a 17 ± 14% loss of their hair while patients in the control group lost 69 ± 32%. Three weeks after receiving cumulative doses of less than 180–315 mg/m^2 of adriamycin, patients in the experimental group had lost only 0.3 ± 0.6% of their hair. As cumulative doses of adriamycin approached 180 mg/m^2, patients in the control group experienced almost total hair loss.

Discussion

Analysis of the data demonstrated that the tourniquet procedure tested in this study reduced the amount of hair loss usually experienced by patients receiving cumulative doses of 180–315 mg/m^2 of adriamycin. The fact that some hair was lost probably indicates that some blood vessels were not totally occluded.

The procedure was well tolerated by patients up to 10 minutes. After 10 minutes, some patients became increasingly aware of time. One patient, however, wanted the tourniquet "tighter," and another refused therapy without the tourniquet. Only one subject chose to withdraw from the study. Her decision to do so may have been influenced by the fact that she was experiencing an exacerbation of her disease process and had previously experienced chemotherapy-induced alopecia.

Those patients in the study who did not receive the tourniquet treatment exhibited self-depreciating behaviors on experiencing marked hair loss. One patient became extremely depressed.

Patients in the study who did not receive the tourniquet treatment exhibited self-deprecatory behaviors on experiencing marked hair loss.

Due to the small sample size, generalizing the results of this study may be limited. Certain variables, such as previous chemotherapy, previous radiation treatments, or infusion rates were not controlled; this further limits the generalizablity of the findings.

Replication of the study with a larger sample and control for between-patient differences is recommended. The effectiveness of this procedure in preventing hair loss at cumulative dose higher and lower than 180–315 mg/m^2 of adriamycin should also be tested. Future investigations should include further testing of time–pressure parameters to determine the most effective and comfortable procedure. □

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