New Chemotherapeutic Agents . . .
Bleomycin and Adriamycin

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Bleomycin

Following extensive, joint evaluation by the National Cancer Institute and the Bristol Laboratories Division of Bristol-Myers Company, bleomycin has recently been approved by the Food and Drug Administration for widespread use. Originally isolated from Streptomyces verticillus by Umezawa in Japan, 1,2 bleomycin is composed of sulfur-containing polypeptides that separate by paper chromatography into two large fractions and 11 subfractions. Available evidence suggests that bleomycin acts primarily by inhibiting DNA synthesis and, to a lesser extent, RNA and protein synthesis.

Response Rate

Initial Japanese research found bleomycin effective against malignant lymphomas and all squamous cell carcinomas including tumors of the head and neck, lung, esophagus, uterine cervix and penis. 3-5 Further studies in the United States confirmed bleomycin's clinical activity against lymphomas, squamous cell carcinomas of the head and neck and testes, but unfortunately failed to prove its efficacy against bronchogenic and esophageal cancer.

Bleomycin is uniformly effective against all forms of malignant lymphoma, but the duration of response is brief. (Table 1.) Blum et al., reviewing the cumulative United States experience, found response rates of: 43 percent in Hodgkin's disease (29 of 68 patients); 47 percent in lymphosarcoma (eight of 17 patients); 45 percent in reticulum cell sarcoma (nine of 20 patients). 6

The 29 responders with Hodgkin's disease had a mean duration of response of 3.1 months (range: one to 13 + months). However, 11 of these 29 patients responded for three months or longer. Similar responses occurred in patients with lymphosarcoma, but in those with reticulum cell sarcoma the mean duration was only 1.8 months (range: one to three months). Responsiveness to the drug was usually evident early in treatment and often at doses below 100 mg.; the total dose of bleomycin for responders was 255 mg., with a range of 25 to 570 mg.

The clinical role of bleomycin in the management of patients with lymphoma must still be determined. To date, most patients studied had advanced disease which progressed on other treatment modalities.

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The overall response rate of bleomycin is within the range of such drug regimens as MOPP, BCNU, CCNU and adriamycin, but the duration of response is shorter. However, bleomycin's virtual lack of bone marrow toxicity makes it a valuable drug in patients with severely depleted bone marrow function; it is now being used in conjunction with MOPP for Hodgkin's disease and COP for non-Hodgkin's lymphoma. Evaluative data should soon be available.

In patients with squamous cell carcinoma of the head and neck, bleomycin has shown an overall response rate of 31 percent. When cases of partial response, 25-50 percent tumor shrinkage are excluded, the rate falls to only 15 percent (24 of 158 patients). By anatomic site, responses varied from a high of 72 percent for squamous cell carcinomas of the mouth to 12 percent for tumors of the tongue. (Table 2.) Unfortunately, as in lymphomas, the average length of response is quite brief and of meager clinical value. In addition, bleomycin is somewhat less effective than methotrexate in these tumors, but because of its lack of bone marrow toxicity, bleomycin in combination regimens is currently being evaluated.

### Table 1. Bleomycin: Rate and Duration of Response

| Type of Tumor                          | Percent Response Rate | Mean Duration of Response (Months) |
|----------------------------------------|-----------------------|-----------------------------------|
| Malignant lymphoma                     |                       |                                   |
| Hodgkin's                              | 43                    | 3.1                               |
| Lymphosarcoma                          | 47                    | 3.1                               |
| Reticulum cell sarcoma                 | 45                    | 1.8                               |
| Squamous cell carcinoma, head and neck | 31                    | 2.0                               |
| Testicular tumors                      |                        |                                   |
| (Bleomycin alone)                      | 32                    | 1.5 – 2.0                         |
| (Bleomycin & vinblastine)              | 90                    | 2.0 – 5.0                         |

### Table 2. Bleomycin: Response Rate in Squamous Cell Carcinoma of Head and Neck

| Anatomical Site | No. Evaluable Patients | Responses | Percent Overall Response Rate |
|----------------|------------------------|-----------|-------------------------------|
|                |                        | Complete  | Partial                       |                              |
|                |                        | >50%      | 25–50%                        |                              |
| Mouth          | 18                     | 3         | 5 5 25 25                       | 72                            |
| Tongue         | 26                     | 0         | 1 2 25 25                       | 12                            |
| Nasopharynx    | 19                     | 2         | 2 2 25 25                       | 32                            |
| Tonsil         | 20                     | 0         | 3 3 25 25                       | 30                            |
| Sinuses        | 10                     | 0         | 2 1 25 25                       | 30                            |
| Larynx         | 37                     | 0         | 4 5 25 25                       | 24                            |
| Other sites    | 28                     | 0         | 2 7 25 25                       | 32                            |
|                | 158                    |           |                               | 31                            |
Table 3. Common Toxic Effects of Bleomycin

| Toxicity   | Percentage Incidence of Toxicity Among Evaluable Cases* |
|------------|--------------------------------------------------------|
|            | U.S. (808) | Japan (540) | E.O.R.T.C. (237) | Scandinavia (154) |
| Mucositis  | 22         | 29          | 26              | 17               |
| Alopecia   | 13         | 20          | 20              | 13               |
| Pigmentation | 8      | 20          | 20              | 16***            |
| Pyrexia    | 26         | 36          | 30              | 36               |
| Anorexia   | 17         | 32          | 32              | 15               |
| Nausea     | 14         | 14          | 14              | 14               |
| Vomiting   | 10         | 10          | 10              | 10               |
| Pulmonary  | 10         | 9***        | 3               | 12               |

*Total evaluable patients in each geographical area shown in parentheses.
**In 72 evaluable patients.
***In 468 evaluable patients.
****In 85 evaluable patients.

The effect of bleomycin alone or in combination with vinblastine for patients with testicular tumors has also been investigated. (Table 1.) In 57 patients studied, the overall response rate was 32 percent with bleomycin alone and 90 percent with the combination therapy. Responses were noted in all cell types but again the duration of response was short for both single agent (1.5 to two months) and for combination regimens (two to five months). This data is now being verified by several groups.

Dosage

The recommended dose schedule for bleomycin is 10-20 mg./m² intravenously or intramuscularly, weekly or biweekly, to a total dose of 400 mg. Dosages in excess of 400 mg. should be approached with great caution in view of the increased risk of fatal pulmonary toxicity.

Clinical Toxicity

Approximately 50 percent of patients experience cutaneous reactions including mouth ulcers, alopecia, hyperpigmentation, thickening, ulceration, redness, hyperkeratosis, nail changes, rash, vesiculation, tenderness, pruritis, hyperesthesia, peeling, stria and bleeding. (Table 3.) Yet in only 0.2 percent of these patients has it been necessary to discontinue bleomycin because of skin toxicity.

The most serious toxic effect of bleomycin is pulmonary toxicity which occurs in about 10 percent of patients. It is extremely difficult to detect as no pathognomonic sign, symptom, X-ray finding or pathologic change have been established. The most frequent manifestation is pneumonitis occasionally progressing to pulmonary fibrosis, which has been fatal in approximately one percent of patients. Bleomycin-induced pneumonitis produces dyspnea and fine rales that mimic those of infectious pneumonias. X-ray examination reveals patchy opacities, usually in the lower lung fields.
Adriamycin

Developed in Italy, adriamycin is a glycoside antibiotic originally isolated by aerobic fermentation of Streptomyces peucetius var. caesius followed by solvent extraction or chromatographic purification. Structurally, it differs from daunorubicin only by hydroxylation of the 14th carbon. It has been theorized that adriamycin acts at the cellular level by binding to DNA and inhibiting RNA synthesis. Adriamycin is effective against a wide range of both solid and hematologic cancers.

Clinical Activity

Breast Cancer

Data suggests that adriamycin may be one of the most active single agents for metastatic adenocarcinoma of the breast. Initial studies found a response rate of 36 percent (44 of 121 patients), equivalent to results achieved with standard agents such as cyclophosphamide (34 percent), methotrexate (33 percent) and 5-fluorouracil (26 percent). The efficacy of adriamycin is even more impressive since most patients studied had not responded to combination chemotherapy with standard agents.

Compared to combination regimens, adriamycin has shown particularly good results as a primary agent in patients with advanced breast cancer. (Table 4.) Southwest Oncology Group compared adriamycin to the five-drug “Cooper regimen” given either continuously or intermittently. Improvement was seen in 55 percent of the adriamycin-treated patients compared to 59 percent of those on the intermittent Cooper regimen and 65 percent on the continuous regimen. The inducing capacity of adriamycin was equivalent to the aggressive five-drug combination. Despite a shorter duration of remission with adriamycin (five months compared to nine and 13.5 months for combinations), it is perhaps the most active single agent for breast cancer.

In a similar study, the Albany Medical College and Roswell Park Memorial Institute compared adriamycin to a three-drug regimen (FCP) of 5-fluo-

| Table 4. Adriamycin Alone Versus Combination Chemotherapy for Advanced Breast Cancer |
|--------------------------------------|--------------------------------------|--------------------------------------|
| **Study Group**                      | **Adriamycin**                       | **Combination**                      |
|                                      | **Dose Schedule**                   | **Response**                         | **Dose Schedule** | **Response** |
| Southwest Oncology Group**           | 60 mg./m² q 3 wks                   | 55%                                 | Cooper Regimen    | 65%          |
|                                      |                                       |                                     | a) continuous    | 65%          |
|                                      |                                       |                                     | b) intermittent  | 59%          |
| Albany-Roswell Park**               | 75 mg./m³ q 3 wks                    | 8 of 23 patients                    | FCP: 5-FU: 8 mg./kg./d x 5 | 13 of 25 patients |
|                                      |                                       |                                     | Cytoxan: 4 mg./kg./d x 5 |                                       |
|                                      |                                       |                                     | Prednisone: 10 mg. tid x 14 q 28 days |
| Mayo Clinic**                       | 60 mg./mg² q 3 wks                   | 9 of 20 patients                    | FCP: 5-FU: 8 mg./kg./d x 5 | 7 of 16 patients |
|                                      |                                       |                                     | Cytoxan: 4 mg./kg./d x 5 |                                       |
|                                      |                                       |                                     | Prednisone: 30 mg./d |                                       |
|                                      |                                       |                                     | FCP + Vincristine (1.4 mg./m² d 1 & 5) | |
rouracil, cytoxan and prednisone, as well as to adrenalectomy. Tumor response was found in eight of 23 patients treated with adriamycin, 13 of 25 patients treated with the three-drug combination and three of nine patients treated by adrenalectomy.

The Mayo Clinic group also compared adriamycin to the FCP regimen used in the Albany study. Regressions were defined as a 50 percent reduction in the product of perpendicular diameters of measurable lesions. Nine of 20 patients responded to adriamycin (45 percent); 12 of 28 patients responded to the combination (43 percent). Toxicity was similar in both groups. Again, the inducing ability of adriamycin was equivalent to the standard combination regimen. Data such as this has encouraged clinical testing of new drug regimens that include adriamycin.

**Sarcomas**

The overall response for adriamycin alone is 26 percent (46/176), with a range of 10 to 40 percent in individual studies. The rate varies according to cell type as demonstrated by the findings for bone sarcomas: 48 percent positive response (14/29) in Ewing’s sarcoma; 35 percent (11/35) in osteogenic sarcoma; 30 to 36 percent in soft tissue sarcoma. Gottlieb et al. have studied adriamycin in combination with 5-(3'-dimethyl-1-triazeno) imidazole-4-carboxamide (DTIC, DIC), another investigational drug which shows slight activity against sarcomas. The drugs in this combination are synergistic in L1210 and P388 murine tumor model systems (data of Drug Evaluation Branch, DCT, NCI). Clinically, both drugs can be given in combination at doses nearly equivalent to those used for each alone. In good-risk patients, adriamycin is administered at 60 mg./m² on day one and DTIC is given at 250 mg./m²/day for five days. Of 200 sarcoma patients currently evaluable, 85 achieved an objective response (43 percent). The addition of vincristine to the adriamycin-DTIC combination regimen has not improved the induction rate (42 percent in 107 patients), but may be increasing survival time. Recently, Gottlieb et al. added cytoxan to the regimen, which is given in 21-day courses as follows:

- **Adriamycin**: 50 mg./m² IV Day 1
- **Cytoxan**: 500 mg./m² IV Day 1
- **DIC**: 250 mg./m² IV Day 1-5
- **Vincristine**: 1 mg./m² IV Day 1-5

A 60 percent overall response rate and long remissions have been reported in 82 patients. Currently, nine different combinations using adriamycin have been or are being evaluated for patients with metastatic sarcomas. (Table 5.)

Of special interest are studies evaluating adriamycin as a surgical adjuvant in patients with osteogenic sarcoma in the hope of improving very low cure rates.

| Table 5. Adriamycin in Combination Therapy for Sarcomas (Under Study) |
|-----------------------------------------------|
| Adriamycin + DTIC |
| Adriamycin + Methotrexate |
| Adriamycin + Vincristine |
| Adriamycin + DTIC + Vincristine |
| Adriamycin + DTIC + VM26 |
| Adriamycin + Vincristine + Cytoxan |
| Adriamycin + DTIC + Vincristine + Cytoxan |
| Adriamycin + Actinomycin D + Vincristine + Cytoxan |
| Adriamycin + Actinomycin D + Cytoxan + Vincristine (2-drug sequential) |
Acute Leukemia Group B is administering adriamycin four to 14 days after radical amputation of the primary tumor; six courses of the drug (30 mg./m² x 3 days) are given every 28 days for a total dose of 540 mg./m². Twenty patients have been observed from 0.5 to 23+ months; five patients relapsed in 0.5 to 20.5 months, and each had violated protocol specifications either by increasing the interval between courses or decreasing the dosage. All 13 patients who followed the protocol exactly, as well as two who did not, are free of evident disease one to 23 months or more after starting the drug (median: 5.5 months). These data demonstrate the possible effectiveness of adriamycin in delaying clinical evidence of metastases from osteogenic sarcoma.

Bronchogenic Carcinoma

Because lung cancer is so resistant, even chemotherapeutic agents which produce responses below the generally accepted criterion (more than 50 percent objective reduction in tumor mass) are often clinically useful. Thus, a reported response rate of 19 percent in 229 patients treated with adriamycin alone (calculated in the usual manner), increases to 26 percent when responses of less than 50 percent objective tumor reduction are included. Furthermore, adriamycin appears to be equally effective in all cell types of bronchogenic carcinoma. Within the limitations of historical comparisons and including cases of less than 50 percent regressions, adriamycin ranks among the most effective drugs for lung cancer: mechlorethamine (36 percent); CCNU (27 percent); mechlorethamine (25 percent); cyclophosphamide (23 percent); hexamethylmelamine (20 percent). Various groups are now evaluating combination regimens that include adriamycin for the treatment of bronchogenic carcinoma.

Malignant Lymphomas

Adriamycin has shown significant activity against all malignant lymphomas with an overall response rate of 41 percent (61 of 147 patients); 36 percent (23/64) in Hodgkin's disease; 56 percent (19/34) in reticulum cell sarcoma; 34 percent (12/35) in lymphosarcoma. Adriamycin could be considered inferior by retrospective comparison with other active agents. However, most of the adriamycin-treated patients had advanced disease and had probably failed standard therapy including combination chemotherapy. In such a patient population, the response rate could be significant since it suggests a very low level of cross-resistance between adriamycin and other agents. For this reason, adriamycin is being considered for patients refractory to other drugs and in new drug combinations.

The Southwest Oncology Group has developed a four-drug combination program (CHOP) for patients with non-Hodgkin's lymphoma which they compared to a three-drug regimen (HOP). (Table 6.) The overall response rate was 85 percent for the 86 patients in both regimens. The complete response rate was 67 percent in 39 CHOP patients and 62 percent in 47 HOP patients; the partial response rate was 18 percent for CHOP and 23 percent for HOP. In patients with histiocytic lymphomas, the complete response rate was 69 percent with CHOP and 70 percent with HOP, while in 15 patients with well-differentiated lymphocytic lymphoma treated with CHOP, the complete response rate was 73 percent. Thus, adriamycin as used in these combinations currently ranks as one of the most effective chemotherapeutic approaches for non-Hodgkin's lymphoma.

Acute Leukemia

Adriamycin has proven effective against both types of acute leukemia with a 24 percent complete response rate (47/195) in refractory patients. By cell type, 24 percent of patients (36/148) with acute lymphocytic leukemia had a complete regression; the overall
response rate was 39 percent (58/148). In patients with acute myelocytic leukemia, the complete response rate was 23 percent.

Other Tumors
Adriamycin has been found effective against a wide range of genitourinary tract tumors. In bladder cancer, the overall response rate is 33 percent (17/52); 5-FU, with a 35 percent response rate, is the only other agent that has been adequately studied. For testicular tumors, predominantly the non-seminomatous types, the overall response rate is 18 percent (7/39). Other studies are currently under way to develop additional data on testicular tumors. The Southwest Oncology Group has reported that two of nine patients with adenocarcinomas of the prostate responded to adriamycin.

In multiple myeloma, the Southwest Oncology Group elicited two responses to adriamycin in 21 patients who had failed other treatments. This group is now studying adriamycin in combination with melphalan and prednisone for patients with multiple myeloma.

Adriamycin has been more extensively studied than any other antineoplastic agent for thyroid cancer. Thus far, the overall response rate is 45 percent (10/22). In fact, adriamycin could be considered the drug of choice for progressive metastatic thyroid cancer on the basis of its known effectiveness and the lack of positive data on other agents. Adriamycin may become the reference drug for trials of more conventional chemotherapeutic agents.

General Toxic Effects
The toxic effects of adriamycin are dose-related, predictable and reversible. Relatively minor side effects include local tissue necrosis, alopecia, nausea and/or vomiting. (Table 7.)

Extravasation during intravenous administration may, without normal precautions, produce local tissue necrosis. Alopecia involving the scalp, axillary and pubic hair occurs in virtually all patients; however, growth usually resumes

| Drug Regimen | No. of Patients | Percent Complete Response Rate | Percent Partial Response Rate |
|--------------|----------------|--------------------------------|-----------------------------|
| **CHOP**     |                |                                |                             |
| Adriamycin (50 mg./m² IV, d1) | 39 | 67 | 18 |
| Cytoxan (750 mg./m² IV, d1) | | | |
| Vincristine (1.4 mg./m² IV, d1) | | | |
| Prednisone (100 mg./m² PO, d1-5) | | | |
| **HOP**      |                |                                |                             |
| Adriamycin (80 mg./m², d1) | 47 | 62 | 23 |
| Vincristine (1.4 mg./m² IV, d1) | | | |
| Prednisone (100 mg./m² PO, d1-5) | | | |
| Every 2-3 week cycles | | | |
after cessation of the drug. Gastrointestinal toxicities evidenced by nausea and occasional vomiting are experienced by 20 to 55 percent of patients but rarely limit clinical use of adriamycin. Only four of 404 patients in a large cooperative study refused further therapy because of GI effects.24

More serious toxic effects include stomatitis and hematologic toxicities. Drug-induced stomatitis occurs in up to 80 percent of patients and typically begins as a burning sensation with erythema of the oral mucosa which may produce ulceration in two to three days particularly in the sublingual and lateral tongue margins. Evidence indicates that stomatitis may develop less frequently as the interval increases between doses.19,40 Leukopenia is the predominant hematologic toxicity, and its severity depends on the dose of adriamycin and the regenerative capacity of the bone marrow. Thrombocytopenia and anemia occur in the same time-frame as leukopenia but they are not as great a problem. Supportive care for hematologic problems should be available for patients being treated with adriamycin.

A note of caution must be sounded here. Dose reduction is recommended in patients with liver disease, based on pharmacokinetic studies showing prolonged adriamycin plasma half-life and lower urinary excretion in patients with impaired hepatic function. Furthermore, analysis showed more pronounced drug toxicity in patients with liver disease receiving full doses of adriamycin.41

Cardiac Toxicity

By far the most potentially serious reactions involve cardiac irregularities, producing transient EKG abnormalities and/or definite cardiomyopathy. Electrocardiographic changes associated with adriamycin are reported in six to 30 percent of patients. Generally transient, these abnormalities include supraventricular tachyarrhythmias, ventricular extrasystoles and ST-T wave changes which generally occur in the first few days after drug infusion.22,24,28,42 Occasionally, further drug therapy is withheld until the EKG returns to its pretreatment configurations. To date, we are unaware of significant morbidity or mortality due to transient EKG changes, and there is no evidence that these are dose or schedule dependent.

In contrast, drug-induced myocardiopathy produces significant morbidity and mortality. This "pump" failure is dose dependent and shows no apparent relationship to pre-existing heart disease. The clinical presentation and pathophysiology of cardiac damage by adriamycin is indistinguishable from other known cardiomyopathies.43 Although the speed of the clinical course varies, it is most often a rapidly progressing syndrome of congestive heart

| Table 7. Common Toxic Effects of Adriamycin |
|--------------------------------------------|
| Toxicity       | Incidence |
|----------------|-----------|
| Alopecia       | 100%      |
| Nausea/vomiting| 20-55%    |
| Stomatitis     | 80%       |
| Leukopenia     | 60-75%    |
| Cardiac irregularities |         |
| EKG abnormalities | 6-30%   |
| Myocardiopathy | .4-1.2%   |
failure and cardiopulmonary decompensation, including dilation of the heart, pleural effusion and venous congestion. Gilladoga et al. report that adriamycin cardiomopathy may be reversed by conventional medical management.

The pathological findings are limited to changes visible by electron microscopy, most dramatically a marked decrease in the number of myocardial fibris accompanied by mitochondrial changes including swelling, focal membrane thickening and dense inclusions. Other non-specific types of cardiomyopathy include nuclear degeneration, disorganization of the sarcoplasmic reticulum and depletion of glycogen granules.

Congestive heart failure due to drug-induced cardiomyopathy, occurs in approximately one percent of patients. Gottlieb has found an incidence of non-fatal and fatal cardiomyopathy of 0.4 and 1.2 percent respectively. The interval between the last dose of adriamycin and congestive heart failure was from one to six months and was dose dependent. Congestive heart failure rarely occurs in patients receiving less than 500 mg./m² of adriamycin, but it becomes markedly more common at total doses above 550 mg./m² (30 percent).

Furthermore, Gilladoga et al. have recently reported on 40 children who received over 495 mg./m² of adriamycin for seven to 31 months. Of seven children who received either pulmonary and/or mediastinal radiotherapy in addition to total doses of adriamycin between 495-720 mg./m², four developed congestive heart failure. Of 33 children who received no concomitant radiotherapy, three developed congestive heart failure at a total dose of 810 mg., 905 mg. and 1695 mg./m². Among 23 children who received 500 to 800 mg./m², none developed this form of drug toxicity. It appears that children can tolerate higher doses of adriamycin than adults and that incidental radiation to the heart may increase the susceptibility to cardiac toxicity.

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