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General Review

The Clinical Evaluation of Analogues

II. Bleomycins

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Bleomycin is a polypeptide antitumor antibiotic discovered in Japan by Umezawa and evaluated clinically in the same country by Ichikawa. The initial studies by Ichikawa indicated that bleomycin had specific effects against squamous-cell tumors, with activity reported against squamous-cell tumors of the head and neck, cervix, lung, esophagus, and penis.

Bleomycin was a drug eagerly awaited by investigators in the United States. The early clinical reports by Ichikawa (1970) indicated that this antitumor antibiotic was active against a range of solid tumors as well as lymphomas. To Ichikawa belongs the credit of first discovering that bleomycin appeared to have specific effects against squamous-cell tumors, and he reported activity against squamous-cell tumors of the head and neck, cervix, lung, esophagus, and penis (Ichikawa, 1970; Ichikawa et al., 1970). Kimura (1972) was the first to describe activity against the entire range of malignant lymphomas. From the first reports from Japan two crucial aspects of toxicity of this drug were obvious. One was a positive factor and the other a negative one. The positive aspect was that bleomycin did not have significant myelosuppressive effects. This opened up many prospects for combination approaches, which still dominate clinical trials with this agent to date. The second aspect of the toxicity was pulmonary side effects, which began as pneumonitis and progressed to pulmonary fibrosis, which could be fatal. Many studies since then have attempted to predict the toxicity or ameliorate it, while vigorous analogue development has been pursued with the aim of finding a compound that would not have this toxicity.

Studies in the United States confirmed most of the original Japanese findings (Blum et al., 1973; Carter, 1976; Carter and Blum, 1976).

The phase I studies in the U.S. revealed a toxicity pattern identical with that reported by the Japanese. Skin toxicity was often dose-limiting, while bone marrow toxicity was rarely severe, if present at all. The pulmonary toxicity was also rapidly recognized as the factor that would limit chronic usage of the drug and would also prevent high doses from being clinically cost-effective.

The phase II studies in the United States confirmed the previously reported activity in squamous head and neck tumors, squamous lesions of the cervix, and in the lymphomas. The single-agent activity was characterized by remissions that were mostly partial in character and were of short duration. While these remissions were not of dramatic clinical benefit, they did indicate the potential value of combination studies. Activity in lung cancer and esophageal cancer was minimal in the U.S. studies, and as a single agent this drug has to be deemed inactive within the clinical setting in which it was evaluated. Activity in testicular cancer was found to be an additional indication for bleomycin, and combination studies with vinblastine have proven that this is one of the areas in which the most significant effects are found with the compound.

Testicular cancer must probably rank as the tumor in which the greatest triumph with bleomycin in combination has been achieved; Samuels (Samuels, 1975; Samuels et al., 1973) was the first to combine bleomycin with vinblastine, and he observed a significant increase in response rate. This increase in response rate included complete remissions, in some of which disease-free periods were of such length that the achievement of cure became a reasonable assumption. This was followed by the studies by Golbey's team (Silvay et al., 1973; Cvitkovic et al., 1974 and 1975), who first added actinomycin D to velban and bleomycin (VAB I), then platinum to these three (VAB II), and then adriamycin and cytoxan to the first four (VAB III). The VAB III (II) regimen also was shown to be highly effective, with nearly everyone treated responding to some degree, and with a high percentage of complete response. Both Samuels and

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Golbey found that giving bleomycin by continuous infusion in this setting appeared to enhance its effectiveness. Einhorn et al. (1976) were able to demonstrate dramatic effects with just velban, bleomycin, and platinum, and others have studied additional approaches. What is clear is that advanced testicular cancer is now a potentially curable lesion with highly aggressive combination chemotherapy.

The malignant lymphomas represent another group of malignancies for which bleomycin has been incorporated into many combinations. In Hodgkin's disease bleomycin has been integrated into primary therapy in two major ways. One approach has been to add bleomycin to the MOPP combination. This has been studied by the Southwest Oncology Group (SWOG) under the study chairmanship of Coltman (personal communication). Published reports have indicated a higher complete response rate in subjects receiving low-dose bleomycin plus MOPP than in concomitant controls treated with MOPP alone.

A second approach in Hodgkin's disease has been to utilize bleomycin in combinations that would be non-cross-resistant with MOPP. Bonadonna et al. (1975) devised a four-drug regimen called ABVD, which utilized adriamycin, bleomycin, vinblastine, and dacarbazine (DTIC). He has shown ABVD to be equivalent to MOPP for induction, and non-cross-resistant. Current studies involve fixed sequences of MOPP and ABVD. The cancer and leukemia group B (CALGB) is studying a combination in which streptozotocin is substituted for dacarbazine in the ABVD combination.

In the non-Hogkin's lymphomas the same two trends can be observed. Bleomycin has been added to the three-drug regimen of cyclophosphamide, vincristine, and prednisone, which is called either CVP or COP, depending upon how the alkylating agent is given. Several groups have added adriamycin too as a fifth drug, and high complete response rates are reported in diffuse histocytic lymphomas and others with poor risk histologies (Schein et al., 1975). It appears that these more aggressive five-drug regimens can give a higher percentage of long-term complete responses that can be considered cures than has been observed with COP or CVP.

Bonadonna and Monfardini (1974) have reported on an ABV combination which can be seen as interacting with CVP in a similar manner to ABVD and MOPP. ABV is ABVD without the dacarbazine.

In head and neck cancer, combinations have not been so extensively evaluated (Goldsmith and Carter, 1975). Only a few series of aggressive combinations with bleomycin have been reported, none of which has been established as clearly superior to methotrexate alone, which has to be considered as the standard for this disease. The combination of bleomycin with radiation for these tumors has been evaluated in many countries. This has an experimental as well as a clinical rationale, but has not been broven synergistic in clinical practice.

Cancer of the uterine cervix is a tumor in which chemotherapy has been relatively neglected until recently (Wasserman and Carter, 1977). Bleomycin has been incorporated into a three-drug combination with mitomycin C and vincristine. Studies in the U.S. by Baker and studies in Japan by Miyamoto indicate that this regimen may be significantly more active in terms of regression than is single-agent therapy.

Despite the fact that single-agent activity in bronchogenic carcinoma was disappointing, many combinations have been attempted because of the marrow-sparing properties of bleomycin. Highly aggressive regimens such as COMB (Livingston et al., 1975) and BACON (Livingston et al., 1974) in squamous lesions gave a higher response rate than single-agent therapy, but without any improved survival, so that these regimens cannot be recommended.

The incidence of bleomycin toxicity varies according to the criteria used for definition. The incidence in reported series ranges from 0–40%. Crooke and Bradner, in a recent review, have tabulated the results of 14 studies which involved a total of 1,890 patients (Comis, in press 1978). The overall morbidity from bleomycin therapy occurred in 11% of the reported cases. Deaths due to bleomycin-induced pulmonary toxicity occurred in 0–6% of these cases. Examination of the dose-level correlation shows that the incidence is low and is consistent with doses of 100–500 units of bleomycin. There does appear to be a significant increase in the incidence when doses in excess of 500 units are given. Thus the pulmonary toxicity of this drug is unpredictable and not dose-related with total doses ranging from 100–500 units. With doses of above 500 mg a threshold appears to be exceeded, and the incidence increases significantly. The findings of a comparable proportion of patients with unexpected autopsy findings indicates that subclinical pulmonary toxicity that can be documented histopathologically occurs with at least the same frequency as clinically significant toxicity.

Several studies are available in which the relationship between bleomycin therapy and changes in pulmonary function tests is evaluated. The tests used most often have included the forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and one-minute single-breath or steady-state carbon monoxide diffusion capacity (DLco). Few studies have evaluated systematic serial determinations or have clearly defined the exact timing of pulmonary function tests relative to the total dose of drug given by the cessation point of therapy. The studies have shown definite changes in TLC, FVC, and DLco after bleomycin ad-

ministration. These changes have revealed no consistent relationships between total bleomycin dose and changes in pulmonary function (Samuels et al., 1976; Pascual et al., 1975; Yagoda et al., 1972).

Recently Izbicki and Baker (1977) and Comis et al. (1977) have reported the results of serial studies with FVC, FEV, and DLco. The preliminary results of both studies show a linear fall in DLco with increasing total doses of bleomycin. Neither study showed a consistent relationship between FVC or FEV determination and total bleomycin dose.

A dry, hacking cough and exertional dyspnea are the earliest symptoms of bleomycin pulmonary toxicity. This can be followed by tachypnea, fever, and cyanosis if the lesion progresses. On physical examination fine crepitant rales can be heard at one or both lung bases, this being one of the earliest signs. With progression there can be coarse bilateral rales, rhonchi, and occasionally the development of a pleural friction rub. As patients progress to respiratory failure intercostal retractions occur.

The initial radiographic sign of pulmonary toxicity secondary to bleomycin is a fine basilar reticular infiltrate. This lesion can resolve with drug cessation or progress with the appearance of bibasilar alveolar-interstitial infiltrates, progressive lower lobe involvement, and finally lobar consolidation.

As discussed previously, there are four ways in which a new analogue could be superior to its parent compound. A bleomycin analogue might show superior activity in responsive tumors or a broader spectrum of activity with activity in tumors that are unresponsive to bleomycin. From a toxicologic point of view an analogue could show either diminished acute toxicity or diminished chronic toxicity. Each of these possibilities requires a particular clinical strategy that is not totally overlapping with any of the other strategies for elucidation.

The phase I study of a new bleomycin analogue will have as its major end-points the determination of a maximally tolerated dose, the elucidation of the acute toxicity pattern, and the determination of any potential biological activity. The crucial decision at the end of the phase I study will be whether a phase II study be undertaken. For a bleomycin analogue the critical comparison will be the acute toxicity pattern of the new drug against that of bleomycin. It is easier to postulate unfavorable acute toxicity potentials for an analogue than to do the reverse (Table 1). Should an analogue have bone marrow toxicity this would be a highly negative factor, which might well preclude further study since the lack of marrow toxicity with bleomycin is one of its major toxicologic advantages. Any new qualitative acute toxicity would be unfortunate in an analogue. An analogue with diminished skin toxicity or stomatitis would be helpful, but in reality acute toxicity would not be an end-point of significant emphasis for a new bleomycin analogue. What it would be critical to look for in the phase I study would be any hint of pulmonary toxicity, which would be a negative factor, and any antitumor responses, which would be a positive factor.

Table 1. Acute toxicity potentials for a bleomycin analogue

Favorable
1. Diminished skin toxicity
2. Diminished stomatitis
3. Diminished nausea & vomiting
Unfavorable
1. Marrow toxicity[a]
2. Increased skin toxicity
3. Increased gastrointestinal toxicity
4. New qualitative toxicity e.g., liver, renal, CNS, etc.[a]

[a] Major factor

Table 2. Bleomycin-responsive tumors

Part of combinations	Single-agent usage predominant
Testicular carcinoma	Head and neck cancer
Hodgkins disease	
Non-hodgkins lymphoma	Cancer of uterine cervix

The phase II trials with a bleomycin analogue would be in bleomycin-responsive tumors, bleomycin-resistant tumors, or a mixture of both. The end-point for phase II study in bleomycin-responsive tumors would be evidence of enough activity to make one feel that the analogue could prove to have a superior therapeutic index after more extensive phase III trials. One problem that exists with phase II trials in bleomycin-responsive tumors is bleomycin's role in combination regimens for some of these tumors (Table 2). A new analogue could possibly be tried in fresh cases of head and neck cancer and cancer of the uterine cervix, but if some of the newer combinations for these tumors can be confirmed as active then fresh cases will no longer be available for these tumor types.

It is difficult to contemplate how to evaluate a new bleomycin analogue in Hodgkin's disease. Some groups use bleomycin in combination with MOPP for initial therapy. Other groups are using the ABVD (adriamycin, bleomycin, vinblastine, DTIC) regimen for either primary therapy or second-line salvage therapy. In either situation a new analogue of bleomycin could only be meaningfully tested for lack of cross-resistance to its parent drug in patients failing to improve on a bleomy-

cin-containing combination. The only possibility would be to seek out groups of patients who had lost their curative potential with chemotherapy after trials of regimens that did not contain bleomycin. These patients would have far advanced disease and be heavily pretreated. In this situation at least a 30% response rate would have to be observed for comparative trials of the analogue in combination regimens to be contemplated.

For non-Hodgkin's lymphoma the situation would be similar, although for this group of lymphomatous malignancies there are many non-bleomycin-containing regimens that are used for curative intent therapy. Patients failing to improve on regimens such as CVP, CHOP, and C-MOPP could be used for phase II evaluation of a new analogue.

Testicular tumors would be the most difficult area in which to plan phase II study. Bleomycin is an essential part of all the major regimens now tried for primary chemotherapeutic attack. Testicular tumors are not common, and patients who have not been exposed to some regimen including vinblastine-bleomycin will become increasingly rare. It may prove necessary to refrain from evaluating any new analogues in testicular carcinomas unless studies in other tumors offer a reasonable hope for a significant improvement in therapeutic index.

Phase II trials in bleomycin-resistant tumors are much simpler to plan for (Table 3). A broader spectrum of activity for a bleomycin analogue could be sought with phase II studies in previously untreated patients with squamous-cell lung cancer, large-bowel cancer, or malignant melanoma. Almost any level of activity with lack of marrow toxicity would make the compound of interest for further study.

Table 3. Bleomycin-resistant tumors for which single-agent phase II studies of an analogue would be reasonable as primary chemotherapy

1. Non-oat-cell lung cancer
2. Large-bowel cancer
3. Pancreatic cancer
4. Malignant melanoma
5. Prostate cancer

Table 4. Possible expressions of decreased pulmonary toxicity of a bleomycin analogue

1. Qualitative
2. Quantitative
   A. Decreased incidence
   B. Decreased severity
   C. Higher dose threshold

The comparative evaluation of a new analogue with bleomycin as regards pulmonary toxicity will be complex (Table 4). Ideally, one would like to have an analogue devoid of pulmonary toxicity; in fact, realistic searching for lower toxicity in some quantitative mode may be more applicable to the current crop of potential analogues for clinical trial. Comparison of the dose level with pulmonary toxicity may not be simple for two reasons: (1) The therapeutic dose schedule of the analogue may not be comparable to that of bleomycin. (2) Bleomycin involves a risk of pulmonary toxicity independent of dose level over a range of 100 to 500 mg before the incidence increases above a 500 mg total dose. The critical aspect of the evaluation will be to determine how many courses of an analogue can be given before the risk of pulmonary toxicity becomes prohibitive, and compare this to the same analysis for bleomycin. Assuming comparable activity, the possibility of maintenance for an additional three months with an analogue would be an advantage.

Evaluation of an analogue for pulmonary toxicity could be approached in the following sequence:

Phase I Study. Since pulmonary toxicity can occur at low doses with bleomycin, the lack of any pulmonary toxicity in phase I study would be a hopeful sign. A significant incidence of acute pulmonary toxic reactions could well preclude further study. Pulmonary function studies could be performed in the patients who receive a second course, and if the DLco is seen to fall this could also be construed as a negative omen.

Phase II Study. Assuming a minimum of comparable activity an initial analysis could be made for pulmonary toxicity in the responding patients. This would involve careful clinical assessment and might also involve DLco serial study. Autopsy material could be examined for evidence of subclinical pathologic damage. At the end of phase II either complete lack of pulmonary toxicity might be evident or severe toxicity might have been observed, so that a firm positive or negative decision might be possible at the end of this phase. If the results were

Table 5. Correlation of dose schedule and time to achievement of critical total dose of bleomycin

Dose schedule	Time to achievement of critical total dose level	
	300 mg	500 mg
15 mg twice weekly	10 weeks	17 weeks
15 mg weekly	20 weeks	34 weeks
5 mg twice weekly	30 weeks	50 weeks

Table 6. Clinical trial strategy for a bleomycin analogue

I. Diminished acute toxicity
Phase I study
A. If acute tocixity same or increased drop
B. If acute toxicity diminished go on to phase II

Phase II. Study in responsive tumors
A. Activity less, drop
B. Activity equal or higher, go on to phase III

Phase III. Confirm superiority

II. Increased activity in responsive tumors

Phase I Study
A. If acute toxicity greater either qualitatively or quantitatively, drop
B. If acute toxicity equivalent or less, go on to phase II

Phase II. Study in primary squamous tumors of head & neck and uterine cervix and previously treated lymphomas
A. If activity less or equivalent, drop
B. If activity greater, go on to phase III

Phase III study. Confirm superiority

III. Broader spectrum of activity

Phase I study
If acute toxicity equal or less than bleomycin

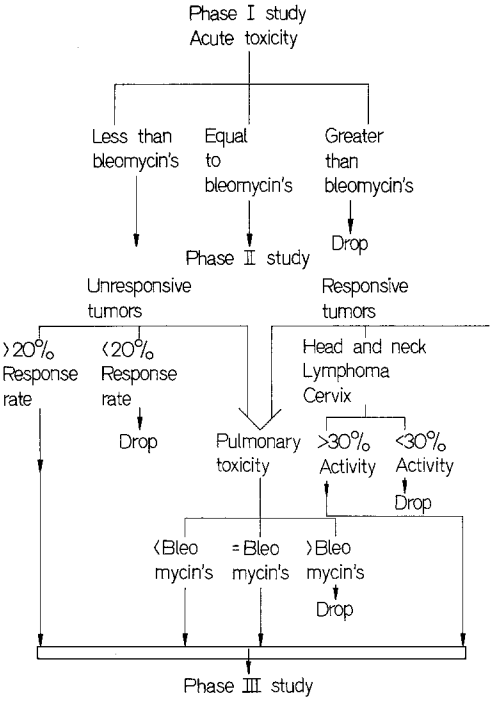
Phase II. Study in non-oat-cell lung, large-bowel, pancreas, melanoma, and prostate cancer
If activity seen, go on to

Phase III

IV. Diminished pulmonary toxicity
Phase I study
If acute toxicity equal or less than bleomycin's and no evidence of pulmonary toxicity observed, go on to
↓
Phase II. Study in responsive tumors

If equivalent or greater activity observed with no significant pulmonary, go on to
↓
Phase III study

Table 7. Proposed phase I and II strategy for a bleomycin analogue



more equivocal and the activity were at least comparable, more detailed study would be indicated.

Phase III Study. If the study were a controlled comparison of the analogue and bleomycin there might be a clear equivalence of dose level to duration of therapy determination and the comparison could be made at comparable equivalence levels utilizing several criteria: (1) Incidence of clinical evidence of pulmonary toxicity. (2) Incidence of pathologic evidence of pulmonary toxicity, utilizing as a denominator those autopsied. (3) Incidence of diminished pulmonary function utilizing DLco. If the phase III evaluation did not have a concomitant bleomycin control then the equivalency would have to be worked out with an "historical control" of bleomycin therapy, which would require greater differences before one could feel confident that a true biologic difference had been discovered. If the phase III trials involved the new analogue in combination with other agents this would be another comparability factor that would make matching with an historical control more difficult.

The historical comparison with bleomycin for an analogue is complicated by the fact that bleomycin has been given according to various schedules and at various dose levels, so that an equivalence will not be simple to work out. Table 5 shows three common dose schedules for bleomycin and the time it would take on these schedules to reach a 300-mg or a 500-mg total dose, assuming no dose reductions. The 300-mg level is chosen because it is so prominent in the literature as a critical total dose, especially in the early reports. The 500-mg level is chosen because upon large-scale retrospective analysis it appears to be the critical threshold dose for the incidence of bleomycin pulmonary toxicity to increase. As can be seen, depending on the dose schedule chosen and the total dose level chosen the criti-

cal equivalence duration could be as short as ten weeks and as long as nearly a year.

The clinical evaluation of a new bleomycin analogue will be a complex process. Analogues tend to move quickly into combination study, which gives little time to evaluate them as single agents in comparison to their parent structure. This will be particularly true with a new bleomycin in analogue, since combinations are the major role for this drug due to its lack of marrow toxicity. Table 6 outlines a proposed strategy for evaluation for the four major possibilities that could improve the therapeutic index. These separations are artificial but, hopefully, will help to conceptualize the problem. The clinical evaluation of analogues sometimes seems to progress without any strategy, and so it is hoped that this will be of aid in future planning. An attempt at integrating the strategies for the phase I and II aspect of the evaluation is given in Table 7. The decision points are arbitrary and open to debate. What should not be debatable is the need for a specific analogue evaluation strategy.

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