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Unusual Sensitivity of Ataxia Telangiectasia Cells to Bleomycin[1]

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ABSTRACT

Peripheral blood lymphocytes from four patients with ataxia telangiectasia (AT), an inherited disorder showing, among other features, radiosensitivity and a high frequency of cancers, were shown to be cytogenetically more sensitive to bleomycin than were lymphocytes from both normal individuals and a single patient with xeroderma pigmentosum. With cell survival techniques, a biphasic dose-response curve was seen for both normal and AT fibroblasts, although the AT cells showed a much lower survival. The increased sensitivity to bleomycin in AT cells might be expected since it is a radiomimetic drug, but more importantly the known action of bleomycin in producing DNA strand scission suggests that AT cells might be defective in rejoining a proportion of DNA strand breaks.

INTRODUCTION

Cells from all patients examined with AT[2] have been shown to be radiosensitive by both colony survival (25) and cytogenetic (5, 21, 26) methods. These results suggested a defect in DNA repair, but the rejoining of single- (19, 25, 28) and double- (14, 25) strand breaks induced by ionizing radiation appeared to be the same in AT and normal individuals, as measured by sucrose gradient centrifugation techniques. An indication of a DNA repair defect came from the report that some AT cell strains exhibited a reduced level of γ-ray-induced repair replication under anoxic conditions (20), although sonicates from AT cells do not appear to be different from those of normal cells in their ability to excise some aerobic γ-ray products from exogenous substrates (22). More recently, it has been suggested on the basis of cytogenetic studies that a small fraction of DNA strand breaks remains unrepaired in X-irradiated lymphocytes from AT patients (24). It has also been shown that an extract from AT fibroblasts had a substantially lower capacity for enhancing the priming activity of γ-irradiated DNA for DNA polymerase from *Micrococcus luteus* than did one from normal cells, although it is not known which enzyme acting prior to repair replication is defective (7). In addition to ionizing radiation, there has been one report of a greater sensitivity of AT cells to actinomycin D compared with controls, using the cell survival technique (6). The purpose of our investigation was to demonstrate clearly by cytogenetic and cell survival methods whether AT cells were more sensitive than normal cells to bleomycin. Bleomycin, an antibiotic with strong antitumor activity (30), was chosen because of its radiomimetic action on chromosomes (4, 9). The specific target molecule appears to be DNA (15–17, 29, 30). It has been shown to release bases from purified DNA, disrupt phosphodiester linkages, and destroy the sugar moiety (29). Bleomycin will also induce both single and double DNA strand scission in bacterial and mammalian cells, as shown by sucrose gradients (15, 16) and alkaline elution techniques (8). Using the latter techniques, single-strand breaks in mouse L1210 cells have been shown to repair following bleomycin treatment (8). The antibiotic will not degrade cytoplasmic 28S, 16S, or 4 to 5S RNA intracellularly (11), nor does it affect the structure or function of globin mRNA (11).

The survival of mammalian cells *in vitro* after bleomycin treatment follows a biphasic response; this has been demonstrated in many mammalian cell types (8, 11, 27). Single-strand breaks induced by bleomycin in L1210 cells as shown by alkaline elution patterns indicated that part of the DNA was extensively broken while the remainder was affected to a lesser degree (8). Such biphasic curves differ in shape from those observed after X-irradiation which may be assumed to generate an essentially random distribution of DNA single-strand breaks in cells. Both cell killing and DNA scissions increased with increasing pH (10). The reduction of the colony-forming capacity correlated with DNA single-strand breaks, and this correlation was independent of pH (10).

MATERIALS AND METHODS

Heparinized venous blood was obtained from 4 AT patients, AT2BI, AT8BI, AT11BI, and AT14BI; 1 patient with XP, XP2BI; and 5 controls, Con 405, Con 406, Con 559, Con 643, and Con 670. In 2 AT patients, blood samples were obtained on 2 different occasions, and these are designated AT2BI(i), AT2BI(ii), AT8BI(i), and AT8BI(ii), respectively. Blood cultures were initiated in Ham's F10 medium as previously described (26) or in DME supplemented with 20 mM HEPES buffer, 10% bovine serum, and 1% phytohemagglutinin. They were harvested at 48 hr following a 1-hr treatment with Colcemid. Bleomycin (Lundbeck Ltd., Luton, England) was added to the blood cultures in 0.1 ml distilled water to give the required concentration. Cells treated at 0 hr (G_0) were incubated for 30 min or 1 hr with bleomycin, spun down, washed once with medium, and reincubated until harvesting. Initially in the investigation, cultures were grown in Ham's F10 medium; but for later cultures, a switch to DME with HEPES was made inasmuch as this medium does not contain Cu^{2+} inhibitory to bleomycin and it also affords a better control of pH. For cells treated in G_2, bleomycin was added at 44 hr after culture initiation and left until harvest at 48 hr. Chromosome preparations were made as previously described (26), and where possible 50 cells were analyzed for aberrations.

Fibroblast cultures were from AT patients and controls

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[2] The abbreviations used are: AT, ataxia telangiectasia; XP, xeroderma pigmentosum; DME, Dulbecco's modified Eagle's medium; HEPES buffer, *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid.

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different from those described above and were maintained in DME supplemented with glutamine, 15% fetal calf serum, penicillin (100 IU/ml), and streptomycin (100 μg/ml) in 9-cm Petri dishes. They were trypsinized from the dishes with 0.25% trypsin in Versene, resuspended at an appropriate dilution in complete medium, and replated in 9-cm dishes on a feeder layer of 6×10^4 γ-irradiated (3500 rads) cells of the same strain. The dishes were incubated for 24 hr in 5% CO_2 in air at 37°, and the medium was removed and replaced with medium containing HEPES buffer and different concentrations of bleomycin for 3 or 24 hr. Following treatment, the medium was removed and replaced with complete medium containing HEPES buffer. Medium was changed every 4 to 5 days, and the cells were stained with 1% methylene blue at 15 to 21 days and counted. Plating efficiencies varied from 13 to 33% for the 3 AT strains AT4BI, AT5BI, and AT7BI and from 9 to 42% for the controls (Con BAR, Con HAR, Con PEA).

RESULTS

Spontaneous Chromosome Aberrations in Lymphocytes. The levels of spontaneously occurring chromosome aberrations in untreated AT and control bloods are given in Table 1. The mean level of dicentric chromosomes and fragments was higher in the AT patients than in controls, although the frequency of chromatid gaps and breaks was comparable. Of the 4 AT patients, AT2BI and AT8BI had a clone of cytogenetically abnormal cells (see Patients 1 and 2 in Ref. 18).

Culturing the cells in the presence or absence of HEPES buffer had little effect on the spontaneous levels of aberrations. A single patient with XP (XP2BI) showing defective excision repair following UV irradiation (A. M. R. Taylor, unpublished results) had the same level of spontaneous aberrations as did normals.

Chromosomal Sensitivity to Bleomycin. AT and normal control lymphocytes were treated, either at G_2 for 30 min (4 hr before harvest at 48 hr) with bleomycin, 25 μg/ml, or for the last 4 hr of culture (44 to 48 hr) with bleomycin, 10 or 30 μg/ml. After each treatment, the level of chromatid gaps and breaks was consistently much higher in the AT cells (Table 2). No increase in chromosome type damage was observed. Some cells (<10%) from both normal and AT individuals showed a very high level of chromosome damage, compared with the majority of cells (Table 2). Blood taken on 2 different occasions from 2 AT patients (AT2BI and AT8BI) showed a consistent sensitivity to bleomycin on each occasion (Table 2). Following treatment with bleomycin, 25 μg/ml, for 30 min at the beginning of G_2 or for the last 4 hr of culture, the level of aberrations in AT8BI was observed to be higher than in its sib, AT2BI. This different level of aberrations in these 2 patients was also seen following X-irradiation of lymphocytes (A. M. R. Taylor, unpublished results). Following treatment with either 10- or 30-μg/ml amounts of bleomycin, there is a further increased level of aberrations per cell in AT14BI compared with both the other AT patients and the normal controls (Table 2). The level of induced aberrations in Patient XP2BI is comparable with control values.

There also appears to be a difference in the frequency of aberrations induced at G_0 in AT11BI compared with controls (Table 3) following treatment for 1 hr with bleomycin, 30 μg/ml, at 0 hr. Although the frequency of induced dicentrics may be higher in G_0-treated AT2BI cells than in controls, after allowing for the spontaneous level, it is difficult to see any differences between AT8BI and controls (Table 3).

As with X-rays (24, 26), bleomycin produced a higher level of aberrations following G_2 treatment of AT cells compared with controls, although the differential sensitivity of AT cells to bleomycin was only 2- to 5-fold greater compared with >10-fold following X-irradiation at G_2. After X-irradiation at G_0, a higher level of both chromatid- and chromosome-type aberrations was observed in AT cells compared with controls (24, 26), and an increase in both types of damage was also seen in cells from one patient (AT11BI) following treatment with bleomycin, 30 μg/ml, at G_0. The dose of bleomycin at G_0 gave approximately the same frequency of chromosome aberrations in normals as did 100 rads X-rays; thus a higher dose of the drug may produce a clearer differentiation between AT and control cells.

Fibroblast Survival following Bleomycin Treatment. Survival curves of AT and normal human fibroblasts show the typical biphasic response seen following bleomycin treatment. Three AT patients, AT4BI, AT5BI, and AT7BI, all showed a more pronounced steep component compared with controls, giving an overall lower survival (Chart 1). The D_0 of the steep component is ~0.3 μg/ml for AT cells, compared with ~1 μg/ml for normal cells, giving an approximately 3-fold increase in sensitivity of AT cells in this portion of the curve. Treatment for either 3 hr with up to 10 μg/ml (Chart 1) or 24 hr with up to 5 μg/ml (Chart 1*B*) shows the same differential sensitivity of the AT cells. Within each survival experiment, the AT cells were always more sensitive to bleomycin, although between experiments the 2 sets of curves (AT and normal control) are not

Table 1

Analysis of untreated lymphocyte chromosomes

Patients AT2BI and AT8BI each had a large lymphocyte clone in addition (see Patients 1 and 2 in Ref. 17).

Patient	No. of cells analyzed	No. of rings	No. of dicentrics	No. of fragments	No. of chromatid gaps	No. of chromatid breaks
AT						
AT2BI(i)	100	0	3	1	4	0
AT2BI(ii)[a]	50	0	3	2	3	0
AT8BI(i)	100	1	21	4	11	0
AT8BI(ii)[a]	50	0	11	1	3	0
AT11BI	100	0	0	7	9	3
AT14BI	50	0	2	6	4	0
XP						
XP2BI[a]	50	0	0	0	5	0
Normal controls						
Con 405	50	0	0	0	2	0
Con 406	100	0	0	4	3	0
Con 559	50	0	0	0	0	0
Con 643[a]	50	0	0	0	6	0
Con 670[a]	50	0	0	0	2	0

[a] Blood cultured in DME and HEPES buffer.

Table 2

Analysis of lymphocytes treated with bleomycin during G_2

Patient	No. of cells analyzed	No. of rings	No. of dicentrics	No. of fragments	No. of chromatid gaps	No. of chromatid breaks	No. of chromatid interchanges
Treatment with 25 μg/ml for 30 min at 44 hr, harvested at 48 hr							
AT							
AT2BI(i)	50	0	5	3	102	23	0
AT8BI(i)	48[a]	0	11	16	125	46	3
Normal controls							
Con 405	49[b]	0	0	1	45	9	3
Con 406	50	0	0	1	39	5	0
Treatment with 10 μg/ml for 4 hr (44 hr until harvest at 48 hr)							
AT							
AT2BI(ii)[c]	50	0	5	2	109	19	0
AT8BI(ii)[c]	50	0	12	6	89	14	0
AT14BI[c]	21[b]	0	0	0	56	9	0
Normal controls							
Con 643[c]	49[b]	0	0	3	40	6	0
Con 670	50	0	0	2	44	3	0
Treatment with 30 μg/ml for 4 hr (44 hr until harvest at 48 hr)							
AT							
AT2BI(ii)[c]	48[a]	0	3	4	109	14	0
AT8BI(ii)[c]	46[d]	1	12	7	147	29	0
AT11BI	23[a]	0	0	1	55	29	0
AT14BI[c]	43[d]	0	1	6	184	51	0
XP							
XP2BI[c]	49[b]	0	0	0	44	13	0
Normal controls							
Con 643[c]	50	0	2	2	36	5	0
Con 559	12	0	0	0	11	3	0
Con 670[c]	48[a]	0	2	0	62	13	0

[a] Two additional cells in this culture with >15 gaps and breaks.
[b] One additional cell in this culture with >15 gaps and breaks.
[c] Blood cultured in DME and HEPES buffer.
[d] Four additional cells in this culture with >15 gaps and breaks.

always superimposable (compare Chart 1*A* and Chart 1*B*). This may be due to the sensitivity of bleomycin to changes in pH (10), although every attempt was made to control this by using the HEPES buffering system.

DISCUSSION

Following treatment of AT cells with bleomycin, there is a high level of chromosome aberrations and low survival compared with normals which is similar to that seen following exposure to ionizing radiation (24–26).

The unusual sensitivity of AT cells to bleomycin suggests that these cells may be unable to rejoin the DNA strand breaks induced by the drug. Ionizing radiation can also produce strand breaks as one of its effects on DNA, and it has been hypothesized that the increased frequency of radiation-induced chromosome aberrations in AT cells compared with normals may be due to a small proportion of unrejoined DNA strand breaks (13, 24). Previously published models of chromosome aberration production suggest that the higher level of chromatid-type damage induced at G_2 by a chromosomally radiomimetic chemical such as bleomycin may be interpreted as due to a defect in the repair of double-strand breaks (2, 24). A proportion of both bleomycin- and radiation-induced strand breaks may therefore be unrepaired in AT cells even though the mech-

Table 3

Analysis of lymphocytes treated at G_0 with bleomycin, 30 μg/ml

Patient	No. of cells analyzed	No. of rings	No. of dicentrics	No. of fragments	No. of chromatid gaps	No. of chromatid breaks
AT						
AT2BI(ii)[a]	50	3	19	16	4	0
AT8BI(ii)[a]	50	1	18	9	9	0
AT11BI	50[b]	4	18	32	37	8
Normal controls						
Con 643[a]	50	1	9	17	2	1
Con 559	50[c]	0	4	11	16	2

[a] Blood cultured in DME and HEPES buffer.
[b] One cell with a triradial chromosome.
[c] One cell with a quadricentric chromosome.

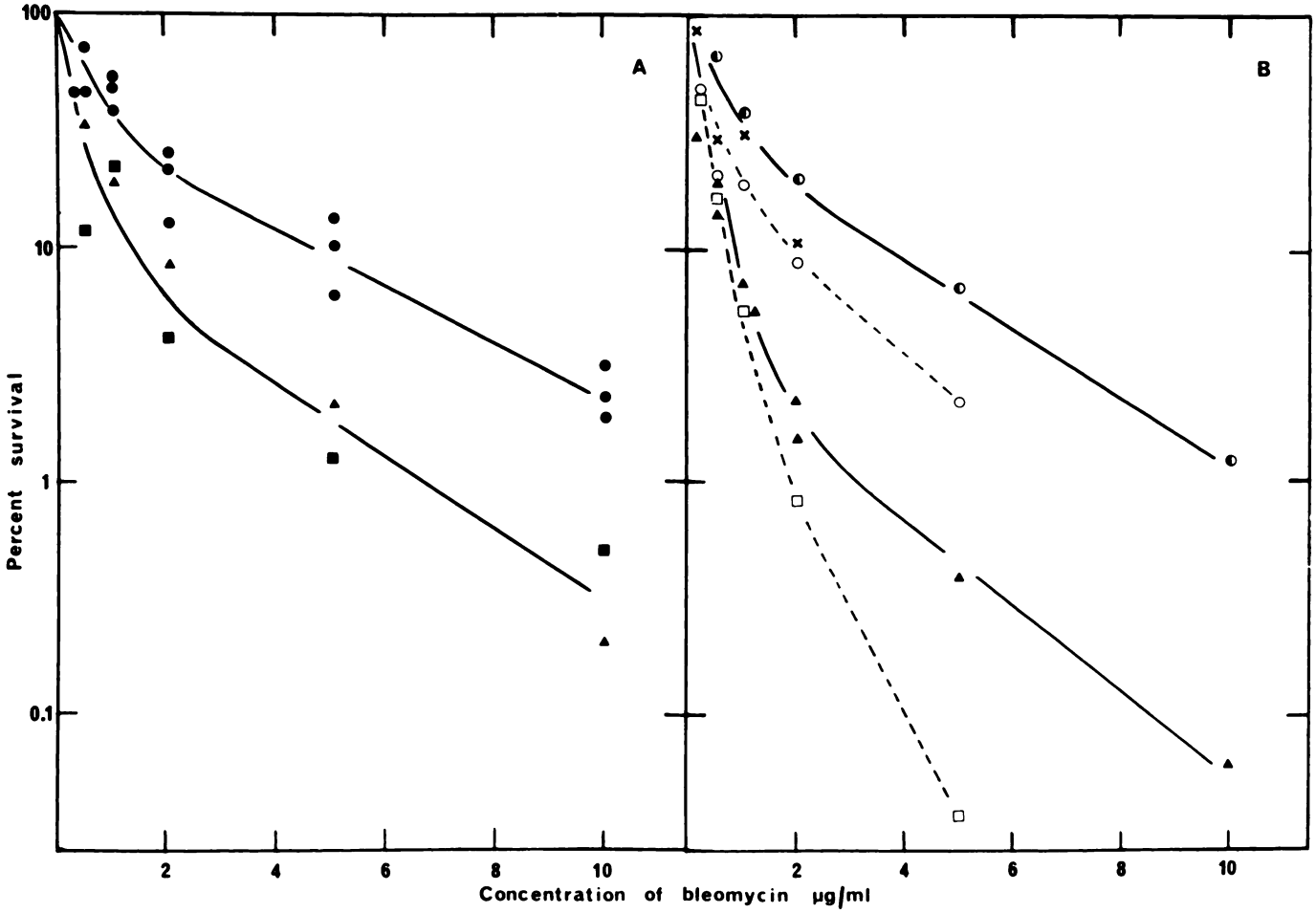

Chart 1. Effect of bleomycin on the survival of AT and normal cells treated simultaneously. *A* compares strains AT4BI (■) and AT7BI (▲) with control Con BAR (●) following a 3-hr treatment. *B* compares in a further experiment the survival of AT7BI (▲) with controls Con HAR (◐) and Con PEA (×) using the same treatment time of 3 hr. A second pair of curves in *B* compares strain AT5BI (□) with control Con BAR (○) following exposure to bleomycin for 24 hr in DME, in the absence of HEPES buffer.

anism by which they arise may be different.

Certain residual unrejoined DNA strand breaks induced by ionizing radiation can be lethal to the cell (19, 23), and it seems likely that double-strand breaks form an important proportion of these (23). However, it has also been reported that nonrejoining breaks in parental DNA serve as permanent barriers to the synthesis of daughter DNA (23). An important consequence of the small proportion of unrepaired single-strand breaks may be that they might give rise to derived double-strand breaks. These would be in addition to the directly induced double-strand breaks.

Single-strand breaks induced by ionizing radiation may be the result of the breakage of different types of bond. At physiological pH, the importance of alkali-labile bonds will be minimal. The formation of breaks by bleomycin may occur by only a single mechanism (16, 17), which could account for the smaller differential effect of bleomycin on AT lymphocyte chromosomes compared with ionizing radiation.

Techniques using sucrose gradient centrifugation have shown that AT and normal cells are no different in their ability to rejoin single- (19, 25, 28) or double- (14, 26) strand breaks induced by ionizing radiation. However, one can reconcile these findings to the suggestion that a small proportion of breaks are indeed unrepaired, since the available biochemical techniques cannot detect differences of rejoining of the order of the 10% required in the hypothesis (13, 24).

It is difficult to reconcile the possibility that all AT patients examined have a proportion of unrepaired DNA strand breaks (13, 24) with the report of Paterson *et al.* (20) that some AT patients are defective in their ability to excise base damage induced by ionizing radiation. Lehmann (13) has discussed this problem with regard to excision proficient and deficient AT individuals and emphasizes the difficulties in interpretation of experimental data.

It has been shown that XP cells responded to bleomycin in the same way as do normal cells with regard to formation and repair of DNA single-strand breaks (8). The normal level of bleomycin-induced chromosome aberrations in XP2BI reported here is also consistent with the notion that XP cells respond normally to bleomycin. The steps in excision repair that are defective in XP cells may therefore not be required for the formation or repair of bleomycin-induced breaks.

The biphasic response curve for bleomycin seen in a range of mammalian cells including cloned cells (27) makes unlikely the explanation in all cases that the resistant

component is due to the presence of genetically resistant cells (27). Neither is the biphasic response apparently dependent on the stage in the cell cycle, although nondividing cells are more sensitive than are logarithmically growing cells (1). A third possibility is that bleomycin induces resistance (27). One can only speculate that the basis of this induced resistance may be due to either a bleomycin-inactivating enzyme or the induction of a DNA repair system (27).

It would be of considerable interest to confirm the observation that bleomycin preferentially attacks internucleosomal DNA, releasing nucleosomes (12) and to discover whether this particular fraction of the DNA is less efficiently repaired in AT cells and what influence chromatin structure had on these processes (3, 31).

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